IN THE FEDERAL COURT OF AUSTRALIA)
NEW SOUTH WALES DISTRICT REGISTRY) No. G 253 of 1987
GENERAL DIVISION)

BETWEEN: AUSTRALIAN FEDERATION OF CONSUMER ORGANISATIONS INC.

Applicant

AND THE TOBACCO INSTITUTE OF AUSTRALIA LIMITED

Respondent

REASONS FOR JUDGMENT

CONTENTS

		Page
1.	Introduction - The advertisement	1
2.	The history of the litigation	4
3.	Was the advertisement published "in trade or commerce"?	5
4.	The meaning of the advertisement	
	(i) Context and class of readers	9
	(ii) Meaning of "evidence"	10
	(iii) Meaning of "scientific proof"	14
5.	Admissibility of evidence to show that statements in advertisement continued to be misleading after date of publication	15
6.	Nature of passive smoking	19

2021550665

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

7. Cancer

(i) Explanation of some epidemiological and other terms 20

(ii) The primary articles
- (a) Trichopoulos 24
- (b) Hirayama - 1981 27
- (c) Hirayama - 1984 27
- (d) Garfinkel 29
- (e) Chan and Fung 30
- (f) Correa 30
- (g) Koo 32
- (h) Buffler 32
- (j) Garfinkel 33
- (k) Akiba 34
- (l) Lee 37
- (m) Humble 37
- (n) Pershagen 39

(iii) The major reviews
- (a) Monograph on Tobacco Smoking issued by the International Agency for Research on Cancer 40
- (b) The National Health and Medical Research Council report on Effect of Passive Smoking on Health 43
- (c) The 1986 Report of the United States Surgeon General 47
- (d) The National Research Council report on Environmental Tobacco Smoke 1986 52
- (e) The Froggatt Committee report 1988 56

(iv) Oral evidence
- (a) Professor Stewart 58
- (b) Professor McMichael 65
- (c) Dr Armstrong 72
- (d) Professor Trichopoulos 76
- (e) Professor Janerich 79
- (f) Sir Richard Doll 81
- (g) Professor Wald 85
- (h) Dr Layard 94
- (j) Professor Tweedie 101
- (k) Professor Witorsch 109
- (l) Professor Huber 113
- (m) Dr Malmfors 118
- (n) Professor Clayton 121
- (o) Mr Leslie 123
- (p) Professor Warren 124

2021550666

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Cancer (cont)

(v) Comments on the epidemiological evidence 124

(vi) Is there more than a little evidence that cigarette smoke causes cancer in non-smokers? 129

(vii) Is there scientific proof that cigarette smoke causes cancer in non-smokers? 133

8. Respiratory disease in young children 140

(i) The primary articles
(a) Harlap and Davies 141
(b) Colley 143
(c) Leeder 148
(d) Sims 150
(e) Rantakallio 151
(f) Fergusson - 1980 152
(g) Fergusson - 1981 154
(h) Ekwo 156
(j) Schenker 156
(k) Ware 157
(l) Pedreira 159
(m) Chen 159
(n) Taylor and Wadsworth 160

(ii) The major reviews
(a) The Surgeon General's report 161
(b) The National Research Council report 164
(c) The National Health and Medical Research Council report 165

(iii) Oral evidence
(a) Professor Landau 167
(b) Dr Le Soeuf 169
(c) Dr Nolan 172
(d) Professor Phelan 173
(e) Professor Witorsch 177
(f) Professor Huber 179

(iv) Does cigarette smoke cause respiratory disease in young children? 182

2021550667

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

9.	Asthma		183
	(i)	Meaning of "asthma"	183
	(ii)	Oral evidence	
		(a) Dr Breslin	185
		(b) Professor Phelan	192
		(c) Dr Le Souef	193
		(d) Professor Witorsch	194
		(e) Professor Huber	195
	(iii)	Conclusion on asthma	196
10.	Otitis Media		
	(i)	Nature of the disease	200
	(ii)	Primary articles	
		(a) Kraemer	200
		(b) Black	203
	(iii)	The major reviews	204
	(iv)	Conclusion	205
11.	Does the advertisement state fact or opinion?		206
12.	Laches, acquiescence and delay		208
13.	Discretion		209
14.	Relief		210

.....

2021550668

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

IN THE FEDERAL COURT OF AUSTRALIA)
)
NEW SOUTH WALES DISTRICT REGISTRY) No G 253 of 1987
)
GENERAL DIVISION)

BETWEEN: AUSTRALIAN FEDERATION OF CONSUMER ORGANISATIONS INC.

Applicant

AND THE TOBACCO INSTITUTE OF AUSTRALIA LIMITED

Respondent

Morling J. 7 February 1991

REASONS FOR JUDGMENT

1. Introduction - the advertisement

In a letter written in 1606 by a Doctor of Physic to a Gentleman it was asserted that tobacco was:

"1. *Not safe for youth*
2. *It shorteneth life*
3. *It breedeth many diseases*
4. *It breedeth melancholy*
5. *It hurteth the mind*
6. *It is ill for the smokers issue.*"

(British Journal of Preventive and Social Medicine (1973), 27, 150).

Nearly four centuries after the Doctor of Physic wrote his letter the debate about the alleged harmful effects of tobacco continues. The applicant claims that the respondent has engaged in conduct that is misleading or deceptive or is likely

2021550669

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

to mislead or deceive in contravention of s.52 of the Trade Practices Act 1974 ("the Act"). The alleged contravention is claimed to have occurred by reason of the publication of an advertisement on 1 July 1986 in several newspapers distributed in Australia. It is not in issue that the respondent caused the advertisement to be published. The advertisement was in the following terms:

"A message from those who do ...
to those who don't

Some non-smokers are annoyed by cigarette smoke. This is a reality that's been with us for a long time.

Lately, however, many non-smokers have been led to believe that cigarette smoke in the air can actually cause disease.

And yet there is little evidence and nothing which proves scientifically that cigarette smoke causes disease in non-smokers.

The London Times reported findings from the Institute of Cancer Research in Surrey, England, published in this month's edition of the 'British Journal of Cancer,' that 'passive smoking' for life-long non-smokers carries no significant increase in the risk of lung cancer, bronchitis or heart disease (all allegedly associated with smoking).

The Institute's conclusions are based on a wealth of statistical detail from a study involving 12,000 people.

In a study by a Vice-President of the American Cancer Society in 1981 which involved 175,000 people, it was reported that 'passive smoking' had 'very little, if any' effect on lung cancer rates among non-smokers.

In the follow-up study published in 1985, no statistically significant increase in risk was reported.

Researchers at the Harvard School of Public Health found that a non-smoker would have to spend 100 hours straight in the smokiest bar to 'absorb' the equivalent of a single filter tip cigarette.

Major reviews on 'passive smoking' over the last few years have concluded that 'passive smoking' cannot be shown to be a health risk. The weight of evidence is summed up in the remarks at the conclusion of the 1984 Vienna Health Conference which was held in co-operation with

2021550670

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

the World Health Organisation: 'should law makers wish to take legislative measures with regard to passive smoking, they will, for the present, not be able to base their efforts on a demonstrated health hazard from passive smoking.'

Often our own concerns about health can take an unproved claim and magnify it out of all proportion; so what begins as a misconception turns into a frightening myth.

Alright, cigarette smoke may be annoying to some non-smokers, but how shall we deal with these problems? Confrontation? Segregation? Legislation?

No.

We think annoyance is neither a government nor a medical problem. It's a people problem. Smokers can help by being more considerate and responsible. Non-smokers can help by being more tolerant. And both groups can help by showing more respect for each others rights and feelings.

Don't let intolerant minority pressure groups use you to create divisions between Australians.

Authorised by John Dollisson,
Tobacco Institute, Gold Fields House, Sydney."

It is the words of the third and fifth paragraphs which the applicant submits are misleading or deceptive or likely to mislead or deceive. The respondent concedes that the words of the fifth paragraph do not give an accurate description of the number of people involved in the study undertaken by the Institute of Cancer Research, and consents to an order restraining the repetition of those words. It resists the claims that the words of the third paragraph are misleading or deceptive or likely to mislead or deceive.

For ease of reference, I shall hereafter refer to the contents of para. 3 of the advertisement as "the statement".

2021550671

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

2. The history of the litigation

On 25 July 1986 the applicant complained to the Trade Practices Commission of the respondent's conduct in publishing the advertisement. On 7 January 1987 the Commission informed the applicant that the respondent had undertaken to run a follow-up advertisement in a form which had been agreed with the Commission and which was accepted by it as a sufficient correction of the original advertisement and that, as a consequence, it considered the matter closed.

The follow-up advertisement was published in January 1987. It did not refer to what was said in the third paragraph of the original advertisement. After referring to other parts of the original advertisement it concluded with the following quotation from remarks made by two scientists at the conclusion of the 1984 Vienna Health Conference:

> *"A drawback in all epidemiological studies up to now consists in the fact that they have been conducted without sufficient quantification of the contamination from passive smoking. Further epidemiological investigations, in which the problem of registering the amount of passive contamination will have to be dealt with more, are urgently needed. New attempts at doing so have been indicated. Since, due to the annoyance connected with passive smoking and the possible hazard to high-risk groups, it also further constitutes a controversial social problem, international co-operation among the various scientific disciplines is the order of the day. Should lawmakers wish to take legislative measures with regard to passive smoking, they will, for the present, not be able to base their efforts on a demonstrated health hazard from passive smoking."*

The applicant was dissatisfied with the terms of the follow-up advertisement and asserted that it did not correct what it claimed to be the misleading and deceptive words of the original advertisement. The applicant sought from the

2021550672

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

respondent undertakings as to the content of future advertisements but the respondent refused to give them.

Thereupon the present proceedings were commenced. By its defence the respondent denies that it has engaged in conduct proscribed by s.52. Further, it relies upon the publication of the follow-up advertisement and an undertaking it has given to the Commission not to re-publish the original advertisement as justification for the Court refusing the relief claimed by the applicant. It also claims that the applicant has been guilty of laches, acquiescence and delay in bringing the proceedings.

The respondent applied to have the statement of claim struck out upon grounds which are no longer material. The application was refused. Leave to appeal against the decision was granted, but the appeal was dismissed: (1988) 19 FCR 469.

3. Was the advertisement published "in trade or commerce"?

It was submitted on behalf of the respondent that in publishing the advertisement it did not engage in conduct in trade or commerce. It was argued that the advertisement should be read as a contribution to the public health debate as to the alleged effect of environmental tobacco smoke on the health of non-smokers and that it has only a tenuous connection with dealings between cigarette manufacturers and distributors on the one hand and smokers on the other. It was argued that conduct is not proscribed by s.52 if it is merely conduct in relation to trade or commerce, that s.52 applies only to conduct in trade or commerce, and that the most

2021550673

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

that can be said of the respondent's conduct in publishing the advertisement is that it was conduct of the former kind.

It was further submitted that there is a great range of plausible circumstances in which people may make statements calculated to affect the lives and pecuniary interests of others. Counsel postulated the example of a campaign in support of higher indirect taxation which, if heeded by government, might affect the price of goods and thus their market appeal. The legislature cannot have intended, so it was submitted, that such political or intellectual activities would constitute conduct in trade or commerce within the meaning of those words in s.52. Such conduct, so it was said, would plainly be conduct which may affect trade or commerce and thus, in one sense, be conduct in relation to trade or commerce but it would not be conduct within the purview of s.52 because it would not be conduct in trade or commerce.

As was pointed out in Concrete Constructions (NSW) Pty Ltd v. Nelson (1990) 64 ALJR 293 at 295 by Mason CJ, Deane, Dawson and Gaudron JJ. the words "trade or commerce" when used in the context of s.52 of the Trade Practices Act are not terms of art but are terms of common knowledge of the widest import. As their Honours there said, the real problem involved in the construction of s.52 arises from the requirement that the conduct to which the section refers be "in" trade or commerce. Their Honours said:

> *"The phrase 'in trade or commerce' in s.52 has a restrictive operation. It qualifies the prohibition against engaging in conduct of the specified kind. As a matter of language, a prohibition against engaging in conduct 'in trade or commerce' can be construed as encompassing conduct in the*

2021550674

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

course of the myriad of activities which are not, of their nature, of a trading or commercial character but which are undertaken in the course of, or as incidental to, the carrying on of an overall trading or commercial business. If the words 'in trade or commerce' in s. 52 are construed in that sense, the provisions of the section would extend, for example, to a case where the misleading or deceptive conduct was a failure by a driver to give the correct handsignal when driving a truck in the course of a corporation's haulage business. It would also extend to a case, such as the present, where the alleged misleading or deceptive conduct consisted of the giving of inaccurate information by one employee to another in the course of carrying on the building activities of a commercial builder. Alternatively, the reference to conduct 'in trade or commerce' in s. 52 can be construed as referring only to conduct which is itself an aspect or element of activities or transactions which, of their nature, bear a trading or commercial character. So construed, to borrow and adapt words used by Dixon J. in a different context in Bank of NSW v. The Commonwealth (1948) 76 CLR 1 at 381, the words 'in trade or commerce' refer to 'the central conception' of trade or commerce and not to the 'immense field of activities' in which corporations may engage in the course of, or for the purposes of, carrying on some overall trading or commercial business.

As a matter of mere language, the arguments favouring and militating against these alternative constructions of s. 52 are fairly evenly balanced. The scope of the prohibition imposed by s.52 is, however, governed not only by 'the terms in which it is created' but by 'the context in which it is found': see Yorke v Lucas (1985) 158 CLR 661 at 668; and, generally, Bank of NSW v. The Commonwealth, at 285. In that regard it is of particular significance that the words 'trade' and 'commerce' have 'about them a chameleon-like hue, readily adapting themselves to their surroundings': O'Brien v. Smolonogov (1983) 53 ALR 107 at 113, quoting Federal Commissioner of Taxation v. Whitfords Beach Pty Ltd (1982) 150 CLR 355 at 378-379. Section 52(2) precludes limiting the scope of s.52(1) by implication drawn from the contents of other provisions of Pt V. Nonetheless, when the section is read in the context provided by other features of the Act, which is 'An Act relating to certain Trade Practices', the narrower (ie the second) of the alternative constructions of the requirement 'in trade or commerce' is the preferable one. Indeed, in the context of Pt V of the Act with its heading 'Consumer Protection', it is plain that s.52 was not intended to extend to all conduct, regardless of its nature, in which a corporation might engage in the course of, or for the purposes of, its overall trading or commercial business. Put differently, the section was not intended to impose, by a side wind, an overlay of Commonwealth law upon every field of legislative control into which a corporation might stray for the purposes of, or in connection with, carrying on its trading or commercial activities. What the section is concerned with is the conduct of a corporation towards persons, be they consumers or not, with whom it (or those whose interests it represents or is seeking to promote) has or may have dealings in the course of those

20215506 75

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

activities or transactions which, of their nature, bear a trading or commercial character. Such conduct includes, of course, promotional activities in relation to, or for the purposes of, the supply of goods or services to actual or potential consumers, be they identified persons or merely an unidentifiable section of the public."

Cigarettes are articles of commerce and restrictions on their use by consumers may render them less attractive as such, resulting in adverse economic consequences for their manufacturers and distributors. No doubt the participation by a trading corporation in a debate on a matter of public or social controversy will often not be conduct in trade or commerce. But the publication of the advertisement in the present case should not be viewed in isolation. It was published by a trading corporation which, so it may be safely inferred, was concerned to ensure that the sale of cigarettes would not be adversely affected by a belief on the part of the public as to a possible causal link between cigarette smoke and disease in non-smokers. The existence of such a link, or of evidence suggesting it, could affect the sale of cigarettes in various ways, e.g. public pressure to restrict the smoking of cigarettes in places where non-smokers are present.

The advertisement had the potential, and was no doubt intended, to protect the commercial interests of cigarette manufacturers and distributors. Accepting that conduct "in trade or commerce" is confined to conduct which is itself an aspect of activities which, of their nature, bear a commercial character I think the proper conclusion is that the publication of the advertisement was conduct "in trade or commerce". Advertising products for sale is an aspect or element of the selling of those products. The selling of the products is indisputably a trading or commercial activity. Advertising may serve a number of purposes. One purpose may be to refute

2021550676

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

criticism of the seller's products thus protecting the market for them. The advertisement published by the respondent was calculated to achieve such a purpose.

To borrow the words used by Dixon J. in Bank of New South Wales v The Commonwealth (1948) 76 CLR 1 at 381 quoted in Concrete Constructions at 295, the publication of the advertisement was an activity within "the central conception" of trade or commerce. In my opinion the publication of the advertisement was conduct "in trade or commerce".

4. The Meaning of the Advertisement

(i) Context and class of readers

The meaning that the words of the third paragraph of the advertisement convey to a reader is of central importance to the case. Much argument was directed to the meaning of the words "evidence", "proves scientifically" and "disease". In my opinion it would be wrong to ascribe a meaning to any of those words, or to the whole paragraph, in isolation from the context in which they are set. As Gibbs C.J. observed in Parkdale Custom Built Furniture Pty Ltd v. Puxu Pty Ltd (1982) 149 C.L.R. 191 at 199, where the conduct complained of consists of words it would not be right to select some words only and to ignore others which provide the context which gives meaning to the particular words.

When considering whether readers would be misled or deceived by the words complained of, regard must be had to the class of persons likely to read the advertisement. The advertisement is directed at the general reading public.

2021550674

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

(ii) Meaning of "evidence"

It is plain that the reference to "evidence" is not a reference only to material that would be admissible in a court of law. Even in the argot of lawyers, "evidence" includes, in some contexts, hearsay material. The first meaning given for the word in the Macquarie Dictionary is "ground for belief". In para. 3 of the advertisement the word is used in the collocation of words "evidence" .... that cigarette smoke causes disease ...." In my opinion many readers would understand the word as referring to data or material which affords grounds for believing that cigarette smoke causes disease in non-smokers. Such material would, in my opinion, include the published results of studies and research work, including collection of data, undertaken by scientists of repute. Many such published results, in the form of articles which have appeared in learned scientific journals, were tendered as part of the applicant's case and I admitted them into evidence.

Articles of this kind were referred to during the course of the case as "primary articles" and it will be convenient to so describe them in these reasons. Some of the primary articles contained comments by the authors on the research work and opinions of others and objection was taken to the admissibility of such comments.

The applicant also tendered a number of reports issued by scientific organisations and professional bodies which have considered the question whether cigarette smoke adversely affects the health of non-smokers. These reports were referred to during the course of the trial as "major reviews" and I shall so describe

2021550678

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

them in these reasons. They included the following: a monograph on the evaluation of the carcinogenic risk of chemicals to humans issued by the International Agency for Research on Cancer, which is part of the World Health Organisation ("the IARC report"); a report of a working party on the effects of passive smoking on health adopted by the Australian National Health and Medical Research Council ("the NH & MRC report"); a report on environmental tobacco smoke by the National Research Council, which is the principal operating agency of the National Academy of Sciences of the United States of America ("the N.R.C. report"); a report made in 1986 by the Surgeon General of the United States of America on the health consequences of involuntary smoking ("the Surgeon General's report"); and the fourth report of the Independent Scientific Committee on Smoking and Health, being a committee appointed by the British Government and chaired by Sir Peter Froggatt ("the Froggatt report").

Mr O'Keefe Q.C., senior counsel for the respondent, submitted that the major reviews were not admissible as opinion evidence to show the state of science nor admissible as evidence of the existence, extent or quality of "evidence .... that cigarette smoke causes disease in non-smokers". He submitted that the passages in the major reviews upon which the applicant relies are based upon nothing more than the work and opinions of other scientists. He contended that the reviews were no more than hearsay out-of-court statements which could not be identified with any particular member or members of the committees responsible for their authorship. In his submission, the reference to "evidence" in the advertisement cannot reasonably be

2021550679

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

understood as referring to opinions expressed by scientists or a group of scientists on the original work of other scientists.

It was also argued that although the primary articles might be admissible to show what had appeared in the scientific literature, they were not admissible to prove the proposition that cigarette smoke causes disease in non-smokers.

I appreciate the force of these arguments, but it is necessary to keep firmly in mind that the question in the present case is whether the statement made in para. 3 of the advertisement is misleading or deceptive or likely to mislead or deceive. In my opinion, many readers of the advertisement would think that the reference to "evidence" is a reference to, inter alia, opinion of competent scientists whether based on their own research or on the published results of the research of others.

First, I think the opinions of competent experts on a matter falling within their field of expertise may afford grounds for belief as to that matter. Many readers (amongst whom would be included the educated as well as the uneducated and the adolescent as well as the mature) would understand such opinions to be evidence relevant to the question whether cigarette smoke causes disease in non-smokers. This understanding would be reinforced by a reading of the entire advertisement. Paragraph 3 is immediately followed by a number of paragraphs in which references are made to published findings and conclusions of scientists and groups of scientists. These references include a statement, in heavy type, that: "Major reviews on 'passive smoking' over the last few years have concluded that passive

2021550680

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

smoking cannot be shown to be a health risk". This statement is in turn followed by a reference to the "weight of evidence" which is said to be ascertained from the summation of views of persons who had attended a Health Conference in Vienna. In my opinion readers of the advertisement would conclude that there is little in the form of published opinions of scientists or groups of scientists to support the proposition that cigarette smoke causes disease in non-smokers. Accordingly, I think the major reviews are admissible to show whether readers would be misled if they reached that conclusion.

My decision in this case would have been the same had I formed a different view as to the admissibility of the major reviews. This is not surprising, since the contents of the primary articles which I admitted into evidence constitute the great bulk of the material upon which the authors of the major reviews base their opinions.

It was submitted that a reader who held the belief that the opinion of a scientist or a group of scientists was "evidence" would not hold that belief as a result of anything said in the advertisement, but rather as a result of his own misconception: cf Pugu at p. 225. There would be something to be said for this argument if the advertisement did not contain references to findings and conclusions of scientists. But the inclusion of those references in the advertisement makes the argument unsustainable.

2021550681

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

(iii) Meaning of "scientific proof"

It is necessary to consider what the phrase "nothing which proves scientifically" conveys to the reader of the advertisement. There was substantial consensus between witnesses that scientists themselves do not commonly use the term "scientific proof". Dr Leslie, a witness called by the respondent said: - "I do not think one ever talks about scientific proof".

Dr Armstrong, a witness called by the applicant, said that every scientist recognises that, at any particular point in time, his knowledge is imperfect and that with the advance of knowledge something which he presently thinks is proven may subsequently be proven to be wrong. He said that scientists accordingly resile from any belief in absolute proof and recognise that proof is relative to the existing state of knowledge. As another witness, Dr Le Souef, said: "The philosophical approach of science is that you cannot absolutely prove anything just as there is no absolute truth."

Nevertheless several witnesses gave what might be called working definitions of scientific proof. Dr Armstrong said: "The only real meaning of scientific proof that I can contribute is that one has a sufficient conviction about the certainty as to take certain consequential actions." The difficulty about this approach is that it gives a variable meaning to scientific proof according to the consequential action that may be called for. Dr Armstrong himself recognised this. As he said (T.1:78):

> *"... I do not believe that there exists any objective or identifiable standard which equals scientific proof. It is very much dependent upon the*

2021550682

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

circumstances for which it is used. In the case of public health measures I would say that the necessary level of proof had been attained when it was considered to be more likely than not that the proposition was true. ... That is good enough when you are dealing with matters pertaining to public health and particularly, and again one would have to qualify this, where the measure that you propose is one which involves the removal of a hazard."

I think an observation made by Dr Witorsch, who was called by the respondent, affords the best guide to a definition of scientific proof. He said, in effect, that scientifically a proposition is proved when the data in support of it is compelling. I do not think Dr Witorsch's approach differs much from that taken by one of the applicant's witnesses, Sir Richard Doll, who thought that scientific proof was proof beyond reasonable doubt or "convincing" scientific proof.

I think that in the context of the advertisement, the words "nothing which proves scientifically that cigarette smoke causes disease in non-smokers" mean "nothing which affords compelling or convincing evidence that cigarette smoke causes disease in non-smokers". This is the meaning which I think most readers would give to the words.

5. Admissibility of evidence to show that statements in advertisement continued to be misleading after date of publication.

The advertisement appeared in newspapers on 1 July 1986. Proceedings were not commenced in this Court until 11 June 1987. On that date an application was filed in which a claim was made for, inter alia, an order in the following terms:

2021550683

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

"1. An injunction restraining th Respondent its servants and agents from, in trade or cc nmerce, engaging in conduct that is misleading or deceptive or is likely to mislead in the following respects:

a. stating that there is lit le evidence and nothing which proves scientific lly that cigarette smoke causes disease in non-si okers;"

In the statement of claim, hich was also filed on 11 June 1987, after references to the publication of the adve tisement and other preliminary matters the allegation is made in para. 6 that, cc trary to the statements contained in the advertisement, it is not the case that the is little evidence and nothing which proves scientifically that cigarette smoke cause disease in non-smokers. There follows an allegation that "in the premises" in or bout July 1986 the respondent engaged in conduct proscribed by s.52. Further a egations are then made that the applicant complained of the respondent's conduct o the Trade Practices Commission, that the Commission thereupon took certain acti n, and that consequent upon that action the respondent published a further advertis ment in which it did nothing to correct the misleading conduct referred to earlie in the statement of claim. Thereafter allegations are made that the applicant sought an undertaking from the respondent "that it would not, in any future advertis ment or promotional material, represent that there is little evidence and nothing wi ch proves scientifically that cigarette smoke causes disease in non-smokers or any similar assertion". Allegations are then made that the respondent declined to provide the undertaking and in the final paragraph (para. 18) it is alleged that: "In the premises, the respondent has continued in trade or commerce to engage in conduct that is misleading, deceptive or is likely to mislead or deceive" in contravention of Section 52 of the Trade Practices Act".

2021550684

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

By its defence the respondent admitted that the undertaking had been sought from it and that it had declined to give it.

At the commencement of the hearing senior counsel for the applicant submitted to the Court a document which, according to him, identified the issues which fell to be determined in the case. One of the issues was said to be whether the statement in para. 3 of the advertisement " ... is and would be true as from the date these proceedings are determined ..." Another issue was said to be whether the statement "was true when these proceedings were commenced in June 1987". In a similar document submitted to the Court by senior counsel for the respondent, one of the issues was said in effect, to be whether the respondent was proposing to re-publish the advertisement.

Relevantly for present purposes, s.80(1) of the Act provides that where the Court is satisfied that a person has engaged or is proposing to engage, in conduct that constitutes or would constitute a contravention of a provision of Part V of the Act (in which s.52 appears) it may grant an injunction in such terms as it determines to be appropriate.

Since no claim for damages was made in the application, I take the essential allegations to be that the respondent on 1 July 1986 engaged in conduct proscribed by s.52, that it had declined to undertake not to engage in similar conduct in the future, and that, accordingly, an injunction was sought pursuant to s.80(1) of the Act to restrain the respondent from engaging in similar conduct.

20215506B5

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

As I have observed, it is alleged in para. 6 that " ... it is not the case that there is little evidence ..." (emphasis added). Having regard to the use of the present tense, this is an allegation as to the state of the evidence at the date of the statement of claim, i.e. 11 June 1987.

However, it was argued on behalf of the respondent that the allegation in para 8 that "In the premises, the Respondent did in or about July 1986, in trade or commerce, engage in conduct that was misleading ..." confines the allegation in para. 6 to the state of affairs that existed on 1 July 1986. It was submitted that because the Court has power under s.80(4)(a) of the Act to grant an injunction restraining a person from engaging in conduct proscribed by s.52, whether or not it appears to the Court that the person intends to engage again in conduct of that kind, the statement of claim should be construed as if there is no allegation that the respondent is proposing to engage in a repetition of past conduct.

I do not think the respondent's construction of the statement of claim is correct. Having regard particularly to the relief claimed in the application, I think it is reasonably plain that what the applicant alleges is that by publishing the advertisement on 1 July 1985 the respondent engaged in conduct proscribed by s.52, that it subsequently did nothing to correct that conduct, that it had refused to give an undertaking not to engage in similar conduct in the future and that accordingly it had continued in trade or commerce to engage in the conduct complained of. It is true that it would have been preferable for para. 18 of the statement of claim to have

0202155068

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

been framed so as to allege that the respondent " has continued and threatens to continue" rather than "has continued". But I think that on a fair reading of para. 18 it contains an allegation that the conduct complained of has continued up to the date of the statement of claim.

I should add that since the grant of the relief sought in the application requires the exercise of the Court's discretion the applicant was entitled to call evidence to prove that the statement remained misleading and deceptive as at the date of trial to persuade the Court to exercise the discretion in its favour.

There was much pre-trial correspondence between the parties in which particulars were sought and given of the allegations in the statement of claim. The respondent argues that this correspondence shows that the applicant particularised its claim in a manner different from the way I interpret the allegations in the statement of claim. There is some imprecision in the particulars given by the applicants but, in my opinion, they do not limit the issues as the respondent contends. Accordingly, the respondent's submission that 1 July 1986 is the only relevant date for examining the correctness of the statement in the advertisement should be rejected.

6. Nature of Passive Smoking:

Passive smoking involves inhalation of tobacco smoke from two sources: sidestream smoke and exhaled mainstream smoke. Sidestream smoke is smoke that is emitted directly from a burning cigarette, pipe or cigar. Mainstream smoke is cigarette smoke which is drawn through the tobacco into the smoker's mouth. The

2021550687

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

term "environmental tobacco smoke" refers to the combination of sidestream smoke and the fraction of exhaled mainstream smoke not retained by the smoker. In contrast with mainstream smoke, environmental tobacco smoke is diluted into a larger volume of air, and it ages prior to inhalation. Mainstream smoke, sidestream smoke and environmental tobacco smoke are sometimes referred to as "MS", "SS" and "ETS" respectively.

7. Cancer

(i) Explanation of some epidemiological and other terms

In support of its case that the statement in para. 3 of the advertisement is misleading or deceptive or likely to mislead or deceive insofar as it relates to the disease of cancer, the applicant relied upon the evidence of a number of witnesses and the primary articles and major reviews to which I have referred. Before referring to the oral evidence it is convenient to set out some of the more important findings referred to in some of the primary articles. An understanding of the articles will be enhanced by a brief explanation of some of the terms used in the literature.

Epidemiology relies on statistical analysis of populations to estimate the incidence of disease amongst those exposed to particular agents. Results are usually reported in terms of odds ratios or relative risk ratios. These reflect the ratio between the frequency of, say, a disease in an exposed group and that in an unexposed group. A risk ratio of 1.0 means that the disease is no more frequent in the exposed group than in the unexposed group. In crude terms, a relative risk above 1.0 is said to be positive and one below 1.0 is said to be negative.

2021550688

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

These results can be characterised as being statistically significant or not. Statistical significance is an expression of the relative confidence that a particular result is a true effect and not due merely to chance. The level of statistical significance conventionally used in the scientific literature is the 95% confidence level. If a result, or range of results, is statistically significant at the 95% confidence level then it means that the probability that those results are due merely to chance or random variation is 1 in 20 or less. The reader can be 95% sure that the true effect is the result as reported.

Often that result is reported as a range of values clustered around a single value called a point estimate. The point estimate is the best estimate of the relative risk, based on the available data. The two figures on either side of the point estimate (the upper and lower confidence limits) define the range of values which are also well supported by the data, at the chosen confidence level. This range is known as the confidence interval.

To take an example, an investigation of the association between exposure (to an agent) and outcome (disease), having opted for a confidence level of 95%, may produce a point estimate of 2.5, with upper and lower confidence limits of 3.5 and 1.5. This means that based on the raw data, the best estimate is that those exposed have a 2½ times greater chance of experiencing the disease than those not exposed. Further, one can be 95% sure that the true relative risk is somewhere between 1.5 and 3.5.

2021550689

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

If the interval between the upper and lower confi nce limits is wide, then the point estimate is less reliable than if it is narrow. Wide onfidence intervals usually indicate a small number of observations.

The final point to note is the relationship between onfidence intervals and statistical significance. The relative risk of disease normally ssociated with pure chance is 1.0: no increased risk, no decreased risk. So, sing say the 95% confidence level, if the value 1.0 lies between the reported upper and lower confidence levels, then the probability that the result is due to c ance has not been satisfactorily excluded, at the 95% level. Whenever the confiden e interval straddles 1.0 then the result is not statistically significant. Two further ill trations may assist. Assume a 95% confidence level. Study A reports a point est. ate of 2.5, with a confidence interval of 1.5 to 3.5. Study B reports a point es nate of 2.5 with a confidence interval of 0.8 to 4.0. The results in study A are st istically significant, those in study B are not.

I set out hereunder brief descriptions of some o he technical terms commonly found in the literature.

Case control study - a group who have a disease (the cases) are selected, and matched to a group who do not (the controls). Researchers then investigate whether or not individuals in each group were exposed to the agent of interest, and those results are then compared. A disease appears first and the investigation of exposure occurs retrospectively.

2021550690

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Cohort study - a group (cohort) of individuals is identified and then divided into those exposed and those who are not. The cohort is followed for a number of years, and the individuals who contract the disease are identified to determine if there is any difference in incidence between the groups. Accordingly, cohort studies are generally prospective.

Dose response relationship - a dose response relationship occurs when the observed incidence of the disease increases as the dose (or exposure to the relevant agent) increases. Such a relationship increases the likelihood that a statistical association in fact represents a true association.

Trend test - a test of statistical significance applied across a set of results to ascertain the probability that such a sequence of results could have been obtained by chance.

Publication bias - due to social, academic and other pressures, it may be that positive research results are written up and/or accepted for publication more frequently than are negative results. This can yield spurious results in meta-analysis.

Misclassification - if subjects are incorrectly classified then it may produce spurious results. The most commonly cited example in this case is the possibility of smokers claiming for a variety of social, medical and other reasons that they are non-smokers. Because of the strong association between active smoking and lung cancer, such misclassification artificially inflates the risk of lung cancer amongst non-smokers.

Confounding - this occurs when sources other than the exposure of interest (e.g. environmental tobacco smoke) operate to affect the outcome, and are not controlled for by researchers. Examples may include work-place pollution, diet, lifestyle, etc.

2021550691

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Data dredging - if within the one study, a number of hypothesised associations are tested, then a high or low result in one particular category might be expected to occur by pure chance. If 20 hypotheses are tested, for example, it would not be surprising to find that one of them is statistically significant at the 95% confidence level. To seize upon such isolated results is said to be data dredging.

Meta-analysis - this is a statistical technique used to combine the results of individual epidemiological studies, in order to derive a quantitative summarisation of data relating to a particular area of investigation.

Mutagenic - a mutagenic substance is a chemical that can induce change in the genetic material in a manner that is thought to be fundamental to the initiation of cancer.

Histological diagnosis of cancer - this biological technique involves obtaining a tissue sample from the patient and examining it under a microscope. It is considered the most reliable form of cancer diagnosis, particularly for distinguishing between primary and secondary cancers.

Cytological diagnosis of cancer - in the case of lung cancer, cytology involves obtaining cells from the lungs either by having the patient cough up cells in the sputum, or washing cells from the lung by use of bronchoalveolar lavage, or extraction with a specialised hollow needle under X-ray control. For a variety of reasons cytological diagnosis of cancer is not considered to be as comprehensive or reliable as histologic diagnosis.

(ii) The primary articles

(a) Trichopoulos et al - Lung Cancer and Passive Smoking

This study was published in the International Journal of Cancer in 1981.

The abstract of the article, as published reads as follows:

2021550692

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

"Fifty-one women with lung cancer and 163 other hospital patients were interviewed regarding the smoking habits of themselves and their husbands. Forty of the lung cancer cases and 149 of the other patients were non-smokers. Among the non-smoking women there was a statistically significant difference between the cancer cases and the other patients with respect to their husbands' smoking habits. Estimates of the relative risk of lung cancer associated with having a husband who smokes were 2.4 for a smoker of less than one pack and 3.4 for women whose husbands smoked more than one pack of cigarettes per day. The limitations of the data are examined; it is evident that further investigation of this issue is warranted."

This was a case-control study, the cases being all of the female, caucasian patients registered as residents of Athens who were admitted to any of three large hospitals in Athens between September 1978 and June 1980 with a final diagnosis of lung cancer other than adenocarcinoma or alveolar carcinoma. Of the 51 cases identified, 14 were histologically and 19 cytologically confirmed. In 18 cases the diagnosis was based on clinical and radiological evidence. A table published as part of the study shows the distribution of non-smoking women with lung cancer and of non-smoking control women according to current smoking habits of their husbands. The published data showed a statistically significant association between the husband's smoking and the woman's lung cancer risk. A non-smoking woman whose husband was a regular smoker had a risk of developing lung cancer which was twice as high as that of a non-smoking woman married to a non-smoker.

The authors of the study stated that it had obvious limitations, most seriously that the numbers of cases was small but that nevertheless the association between passive smoking and lung cancer was unlikely to be due to chance. They drew attention to the fact that, according to their study, the relative risk associated with passive smoking, i.e. 2.4 for all categories of smokers combined, was only slightly

2021550693

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

lower than the figure of 2.9 associated with active smoking by the women themselves. The authors offer a possible explanation for this circumstance in the text of their study.

The study reported in the International Journal of Cancer in 1981 was continued and further results of it were published in The Lancet in September 1983. The authors reported that there were then twice as many cases and 50% more controls in the study, but that the results remained substantially the same. The 1983 study, as published, wrongly calculated the relative risks. The correct relative risks of lung cancer associated with having a husband who smoked were 1.9 for a smoker of less than one pack and 2.5 for women whose husbands smoked more than one pack of cigarettes per day. Professor Trichopoulos explained in oral evidence that the equivalent figures which appeared in the 1983 publication, i.e. 2.4 and 3.4, were typographical errors. The 1983 figures (1.9 and 2.5) relate to the total data collected in the whole of the study, not merely to the data collected since the publication of the first study.

The authors concluded their 1983 study with a reference to a table including the abovementioned risk ratios of 1.9 and 2.5 and stated:

> *"The table increases the credibility of the hypothesis implicating passive smoking as a factor in lung cancer. Given the small size in the relative risk and the many potential sources of bias, no single study will be able to provide convincing evidence for or against this hypothesis; only the convergence of results from different studies in different populations will permit a reasonably sound conclusion. We consider the Athens study a step in this direction."*

2021550694

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

(b) Hirayama - Nonsmoking wives of h avy smokers have a higher risk of lung cancer: a study from Japan

In the British Medical Jour al of January 1981 Professor Hirayama, Chief of the Epidemiology Division of the l ational Cancer Centre Research Institute, Tokyo, published findings of a study un ertaken in Japan. The abstract of the findings as published in the article is as foll ws:

> *"In a study in 29 health centre district in Japan 91 540 non-smoking wives aged 40 and above were followe up for 14 years (1966-79), and standardised mortality rates for lung ancer were assessed according to the smoking habits of their husbands. W ves of heavy smokers were found to have a higher risk of developing lun cancer and a dose-response relation was observed. The relation between he husband's smoking and the wife's risk of developing lung cancer showe l a similar pattern when analysed by age and occupation of the husban The risk was particularly great in agricultural families when the husb nds were aged 40-59 at enrolment. The husbands' smoking habit did nc affect their wives' risk of dying from other disease such as stomach ca cer, cervical cancer, and ischaemic heart disease. The risk of developin emphysema and asthma seemed to be higher in non-smoking wives of eavy smokers but the effect was not statistically significant.*
>
> *The husband's drinking habit seeme l to have no effect on any causes of death in their wives, including lung c ncer.*
>
> *These results indicate the possibl importance of passive or indirect smoking as one of the causal factor of lung cancer. They also appear to explain the long-standing riddle of v hy many women devel p lung cancer although they themselves are non-sr okers. These results c lso cast doubt on the practice of assessing the rel tive risk of developing lung cancer in smokers by comparing them with nc n-smokers."*

(c) Hirayama - Cancer Mortality in N nsmoking Women with Smoking Husbands Based on a Large-Scale Cohort St dy in Japan

This article (which appeare l in Preventive Medicine in 1984) reported further conclusions reached by Professor Hirayama as a result of further data derived

2021550695

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

from his study referred to in the pr ceding article. The abstract of this further study reads as follows:

"Mortality of 91,. 10 no smoking wives was studied in relation to the smoking habits of th r hus nds by means of a cohort study in Japan. During 16 years of f llow-u , 200 deaths from lung cancer took place. The relative risks of ung c ncer in these nonsmoking wives were 1.00, 1.36, 1.42, 1.58, and !.91 v en husbands were nonsmokers, ex-smokers, or daily smokers of 1· 4, 15· 9, or 20 or more cigarettes daily, respectively. Corresponding relativ risks f r stomach cancer were 1.00, 1.16, 1.00, 1.00, and 1.01 respectively. Speci city of association and internal consistencies were observed. Amc g ca ers of each site, a similar tender cy toward risk elevation in non nokin wives with smoking husbands was observed for nasal sinus cance brai tumors, and cancer of all sites besides lung cancer. In interpre ng th se results, the significance of proximity in exposure to sidestrear smok in Japanese homes was stressed."

Professor Hir: ama ade the following observation:

"This study c nfirm the correlation between lung cancer and spousal smoking rep rted eviously. The correlation is quite specific in terms of diseases. F · inst ce, no risk elevation at all was observed for stomach cancer. A rikin internal consistency of association was also observed. The resu wer essentially similar when observed in terms of age of husbands, a of ives, occupation of husbands, and differing periods of observati 1. T e results are in line with a Greek study by Trichopoulos and o. ers a a U.S. study by Correa and others (external consistency), althou the are slightly at variance with an American Cancer Society stu in ie United States and a case-control study conducted by Kabat nd W nder."

The referenc to t e American Cancer Society study is a reference to Garfinkel's study (infra).

2021550696

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Professor Hirayama also obse ved:

"When the effects of passive moking due to husbands' smoking were compared with the effects of d rect smoking in women, the results clearly indicated that the effect of p ssive smoking is less than one-fifth that of direct smoking. ... In terms o attributable risk, however, the effect of passive smoking on lung cancer i women is nearly as important as that of direct smoking because the p opulation of intrahousehold passive smokers at risk is four times greate ... than the population of active smokers... Therefore, although the rel tive risk of indirect smoking is much smaller than that of direct smoking, he absolute excess deaths from lung cancer due to passive smoking may be quite important because of the large size of the exposed group - e pecially in countries such as Japan where the majority (nearly 70%) of a dult men smoke, but only a minority (15% or less) of adult women smoke '

(d) Garfinkel - Time Trends in Lung C ncer Mortality Among Nonsmokers and a Note on Passive Smoking

This article appeared in the ournal of the National Cancer Institute in June 1981.

The author concluded that c mpared to non-smoking women married to non-smoking husbands, non-smokers marri d to smoking husbands showed very little, if any, increased risk of lung cancer. The s udy revealed a small increased risk of lung cancer for non-smokers married to smoke s. The increased risk was not statistically significant. The mortality ratios for lun cancer in non-smoking women were 1.27 when the husbands were daily smokers of less than 20 cigarettes, and 1.10 when they smoked more than 20 cigarettes per day. The data examined by Garfinkel led him to conclude that "it seems doubtful that t ose non-smokers who had been heavily exposed to cigarette smoke from others in their lives could have had many more precursor lesions for the development of lung cancer than non-smokers not so

2021550697

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

exposed. Therefore, there is evidence from these studies that passive sr oking cannot play more than a very small role in the development of lung cancer."

(e) Chan and Fung - Lung Cancer in Non-smokers in Hong Kong

This study was carried out in Hong Kong and was publi ned in 1982. The relevant finding in the study is at variance with that found in the Hirayama 1981 study. Whereas Hirayama found that the mortality from lung cancer of non-smoking women exposed to cigarette smoke of their husband's was increased tw fold, that was not confirmed by this study. The authors acknowledge that the g oup s udied by them was very small in comparison to the group studied by Hirayama.

(f) Correa et al. - Passive Smoking and Lung Cancer

This study appeared in The Lancet in September 1983. Correa et al undertook a case-control study involving 1338 lung cancer patie its and 1393 comparison subjects in Louisiana, USA. They found that non-smol rs married to heavy smokers had an increased risk of lung cancer, as did subjects hose mothers smoked. No association was found between lung cancer risk and pat rnal smoking. The authors said, inter alia,

> *"Spouse-smoking Effect*
>
> *Our data strengthen the contention that heavy smoking by one m nber of the spouse pair increases the lung cancer risk of the non-smoking partner. Heavy smoking by wives may increase the risk of the light smoking husband but this finding requires further analysis and confirmation in larger series. Smoking by husbands did not affect the risk of lung cancer in women who smoked (relative risk 1.03), a finding that suggests that active smoking is so powerful that it overshadows any possible additional effect from concomitant passive exposure.*
>
> ...

2021550698

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

The effect of the smoking h bits of ne spouse on lung cancer risk was first reported by Hirayama i a Japar ese cohort study. A cohort study in the United States reported a positive but not significant increase in risk for non-smoking women mu ried to moking husbands. A case-control study of non-smoking wome diagnos d as having lung cancer in Greece reported relative risks of app ximatel 2.5 for those married to moderate smokers and 3 for those n rried tc heavy smokers, with a significant linear trend. Our numbers are sm l but we think that the similarity between our findings and ose of Trichopolous et al strengthens the suspicion that passive smoki ; may cc tribute to lung cancer risk.

Parental Smoking Effect

As far as we know, our is the fi st case-control study of lung cancer reporting on parental smoi ng histc y. Parents' smoking behaviour influences the smoking hab s of the r offspring, but we found that the smoking behaviour of the fa ier does ot influence the lung cancer risk of his offspring, whereas the b haviour f the mother does. This difference may reflect the closer and m re prolc ged contact that infants and young children have with their mot ers than vith their fathers."

The authors expresse their c nclusion as follows:

"The differences betwee the effe s of passive exposure to spouse and maternal smoking are puzz ng. Pa ive exposure to spouse smoking is mostly detected in non-sm kers an light smoking males; maternal passive smoking effects are s en most in smokers. Passive smoking from spouses is introduced in adu t life an in smokers is concum nt with their own active smoking. The n agnitude of such an effect may be low when compared with active conc mitant sr oking and it may not be detectable when both types of smoking are prese t.

Maternal smoking, on the other h nd, exerts its influences early in life and in the absence of acti e smokin is probably insufficient to produce carcinogenic effects. Our f ndings in icate that maternal smoking results in a slight increase in lung cancer r sk but do not indicate whether the effect is due to enhanced active smo ing of the offspring or to enhanced susceptibility to lung cancer induc ion after the challenge of active smoking later in life."

2021550699

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

(g) Koo et al. - Active and passive smoking among female lung cancer patients and controls in Hong Kong

This was a case control study carried out in Hong Kong and published in 1983. The study, in which the number of cases and controls were fairly small, did not reveal a positive association between lung cancer and passive smoking. The authors observed:

> *"Thus, if passive smoking had contributed to the risk for never smokers, it could only have acted as a co-factor in a multi-factorial aetiology. The controversial findings of various researchers ... on the role of passive smoking in lung cancer could well be due to a failure in identifying other co-factors in the carcinogenesis."*
>
> (The reference to the "various researchers" is a reference to the findings of Garfinkel, Hirayama and Trichopoulos).

(h) Buffler et al. - The Causes of Lung Cancer in Texas

This study was published in 1984 in Lung Cancer: Causes and Prevention. Amongst other results, the authors reported the following:

> *"The role of 'passive smoking' in contributing to risk of lung cancer was examined .... In this analysis the crude (or unadjusted) odds ratio are increased and significant for both males and females, 1.4 and 2.1, respectively. However, when the confounding effect of individual subject smoking was controlled by stratifying the male and female study groups into smokers (ever) and non-smokers (never) and examining the adjusted odds ratios, there was no significant increase in risk associated with passive smoking. In fact, the odds ratio for non-smokers living with a regular smoker were not increased for either males or females, 0.52 and 0.78, respectively. However, odds ratios for smokers living with a regular smoker were increased, although not significantly, 1.28 and 1.80 for males and females. The overall odds ratios (adjusted) associated with passive smoking were only slightly increased and not significant for either females, 1.2 and 1.3, respectively. When the possibility of a 'passive smoking' effect was examined among non-smokers by the number of years lived with a regular smoker, there was very little difference in risk for females who lived with a regular smoker for 0-32 years. The odds ratios for males suggest an increase by [sic] are based on smaller numbers than the analysis in females."*

2021550700

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

The authors noted that the "lack of a 'passive smoking' effect when the confounding effect of smoking of individual study subjects is considered, is not consistent with early reports. Although subsequent reports are also not consistent with regard to this association, it may be that the study population available was not sufficiently large to detect a fairly low-level effect and that this association needs to be assessed in a considerably larger study population".

(j) Garfinkel et al. - Involuntary smoking and lung cancer: A case-control study.

This article appeared in the Journal of the National Cancer Institute in September 1985. The authors state, inter alia:

> *"In a previous paper, we pointed out that in any study of involuntary smoking and lung cancer, categorizing nonsmokers by the smoking habit of the spouse may lead to error in classification of exposure. In the United States particularly, there may be many women, married to nonsmokers, who are exposed to the smoke of others at work or in other areas. Conversely, some individuals married to smokers may suffer acute effects from inhaling smoke and consciously avoid such exposure. A survey of 38,000 subjects by Friedman et al. confirmed this hypothesis. About 40% of women nonsmokers and 50% of men nonsmokers who were married to nonsmokers were exposed to the smoke of others for some periods of time during a week, and 47% of nonsmoking women married to smokers reported that they were not exposed to tobacco smoke at home. In the study reported here, we record the smoking habit of husbands (total No. of cigarettes smoked and No. smoked at home), as well as the number of hours a day the subjects were exposed to the smoke of others at home, at work, and in other areas.*
>
> *Other causes for concern are establishment of the microscopic diagnosis of primary lung cancer and verification of the smoking history. In a study of the histologic type of lung cancer in relation to asbestos exposure, 49 of 774 men and women with a discharge diagnosis of microscopically proved lung cancer were recorded as nonsmokers in the hospital chart. After review of hospital records, histologic sections, and interviews, only 10 cases remained who had died of primary lung cancer and who had never*

2021550701

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

smoked. One-half of the oth ers had smoked at some time and one-half the confirmed nonsmokers h d a primary cancer other than that of the lung.

It is apparent, therefore, tha t more studies on involuntary smoking are needed, with particular atter ion given to obtaining microscopic proof of primary lung cancer and m re detailed information about exposures to cigarette smoke."

The authors undertoo k a case-control study in four hospitals from 1971 to 1981. All cases and controls v ere confirmed by histologic review of slides, and nonsmoking status and exposures ' ere verified by interviews. It was found that odds ratios increased with increasing numbers of cigarettes smoked by the husband, particularly if the cigarettes were s noked at home. The odds ratio for women whose husbands smoked 20 or more ciga ettes at home was 2.11. The authors' conclusions included the following:

"We found an elevated r k of lung cancer, ranging from 13 to 31%, in women exposed to the sm ke of others, although the increase was not statistically significant. Th women who were married to smokers of 40 or more cigarettes a day or who were exposed to the smoke of at least 20 cigarettes a day at home s owed a risk twice as high as that of women not exposed at all. This re lt is consistent with the dose-response risk of exposure to the husband's smoke shown in some case-control studies (2, 3)."

(The references at he end of the above quotation are references to Trichopoulos et al (upra) and Correa et al (supra).

(k) Akiba et al. - Passive Smc king and Lung Cancer among Japanese Women.

This article was p blished in the September 1986 issue of Cancer Research, but appears to have been first published prior to 1 July 1986 since it is referred to in the NH & MRC r port which was adopted in June 1986.

2021550702

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

The abstract of the article, as published, reads as follows:

> *"A case-control study conducted in Hiroshima and Nagasaki, Japan, revealed a 50% increased risk of lung cancer among nonsmoking women whose husbands smoked. The risks tended to increase with amount smoked by the husband, being highest among women who worked outside the home and whose husbands were heavy smokers, and to decrease with cessation of exposure. The findings provide incentive for further evaluation of the relationship between passive smoking and cancer among nonsmokers."*

The study was made as part of a case-control investigation of lung cancer among atomic bomb survivors conducted primarily to evaluate the interactive roles of cigarette smoking and ionizing radiation. Data were collected on the smoking habits of the subjects' spouses and parents. The article reports the effect of exposure to such passive smoking, particularly on married women who had never smoked themselves.

The study showed that there was an increase in lung cancer risk with increasing amounts smoked per day by the husband, with the odds ratio slightly exceeding 2 for women whose husbands were heavy smokers. The odds ratio of lung cancer among non-smoking women according to recency of exposure to their husbands' smoking were lower among women who had not been exposed within the last ten years than among women exposed within the last ten years.

All the results in this study were reported using 90% confidence intervals. The odds ratio for non-smoking females married to smoking husbands was 1.5, statistically significant at that level. For non-smoking husbands married to smoking wives the odds ratio was 1.8, not statistically significant at the 90% level.

2021550703

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

The authors said:

> *"The results from this case-control study suggest that there may be a moderate excess in lung cancer risk associated with passive smoking. The odds ratios for lung cancer among non-smoking women tended to increase with amount smoked by their husbands, a trend seen among housewives as well as women who worked outside the home. The highest odds ratios among nonsmokers were for women who worked in blue collar jobs whose husbands were heavy smokers, women presumably with the highest exposure to environmental tobacco smoke. There was little association with parental smoking or with ex-passive smoking, suggesting that cessation of exposure may lower risk.*
>
> *The findings are generally consistent with results of a national cohort study of mortality among Japanese women and of several epidemiological investigations conducted elsewhere in the world."*

The Japanese study referred to by the authors is the Hirayama 1981 study, and the other studies to which they refer are the Trichopoulos et al 1981 study, the Correa et al 1983 study and the Garfinkel et al 1985 study.

The authors admit to concerns about adequacy of data provided by surrogate respondents and reliability of diagnoses of lung cancer but also note some reassuring factors.

The authors summarise the views they formed as a result of their study as follows:

> *"In summary, the results of this investigation suggest that exposure to environmental tobacco smoke may increase the risk of lung cancer among nonsmokers. The findings, from one of the two areas of the world where the possibility of a passive smoking hazard was first postulated, add to an accumulating body of evidence on the issue. While the total evidence is not definitive and not all studies show significantly positive associations, the results are suggestive enough to warrant further evaluation in larger studies where passive smoking exposures can be more fully quantified."*

2021550704

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

(l)] ee et al. - Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases

This study was published in the British Journal of Cancer in 1986. The author reported results based on 143 patients. They made the following observations:

"Overall the results showed no evidence of an effect of passive smoking on lung cancer incidence among lifelong non-smokers. In male patients, relative risks were increased for some of the indices but numbers of cases were small and none of the differences approached statistical significance. In females, where numbers of cases were larger, such trends as existed tended to be negative .... The relative risk in relation to the spouse smoking during the whole of the marriage was estimated to be 0.80 for the sexes combined, with 95% confidence limits of 0.43 to 1.50."

"In the present study no significant relationship of passive smoking to lung cancer incidence in lifelong non-smokers was seen, either in the analyses based on the information collected in hospital or in subsequent inquiry of the spouses or both. It must be pointed out, however, that the number of lung cancer patients who had never smoked was rather small so that, though our findings are consistent with passive smoking having no effect on lung cancer risk at all, they do not exclude the possibility of a small increase in risk, ... "

(m) Humble et al. - Marriage to a Smoker and Lung Cancer Risk

This study appeared in the American Journal of Public Health in May 1987 In the introduction to their study, the authors make the following statement:

"In 1980 we began collecting data in a population-based case-control study designed to explain differing lung cancer occurrence in Hispanic and non-Hispanic Whites in New Mexico. The original study questionnaire included questions on tobacco smoke exposure from spouse smoking and on indirect exposure to asbestos through a spouse's job. This report describes the risks associated with these exposures in smokers and nonsmokers in New Mexico."

2021550705

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

The authors analysed the data according to two models. On the first model, among never smokers, cigarette smoking by a spouse, regardless of pipe or cigar use, was associated with a three-fold increased risk of lung cancer. (OR 3.2, 90% CI 1.5 - 7.2). For females only the odds ratio was 2.3 with CI 90% 0.9 - 6.6. For exposure to cigarettes only, the odds ratios were slightly lower (for all subjects 2.9 90% CI 1.3 - 6.7; for females only 1.8 90% CI 0.6 - 5.4.

Odds ratios from use of the second model tended to be lower.

No effect was detected for marriage to a smoker by a current or former cigarette smoker, according to either model.

Under the heading "Discussion", the authors made the following observations:

> *"In the context of a population-based case-control study in New Mexico, we have examined the risk of lung cancer associated with marriage to a cigarette smoker. The results indicated increased risk from this exposure in never smokers, but not in active smokers.*
>
> *Methodologic limitations of the case-control approach for studying the relation between involuntary exposure to tobacco smoke and lung cancer must be considered. Misclassification of both active and passive exposure to cigarette smoke is of particular concern."*

In conclusion, the authors made the following comments:

> *"The results of the present case-control study complement those from other case-control studies and from cohort studies, which showed increased lung cancer risks in never smokers married to smokers. The magnitude of the effect of marriage to a smoker in the present study, about a the two-fold increase in risk ... is comparable to findings by*

2021550706

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Hirayama and by Akiba, et al, in Japan, by Trichopoulos, et al, in Greece, and by Correa, et al, and by Dalager, et al, in the United States. A weak exposure-response relation was present with duration of passive exposure, but not with average number of cigarettes smoked daily by the spouse ...

In active smokers, we found that residence with a smoker did not elevate lung cancer risk ... The lack of association in active smokers is consistent with the quantitative differences in the exposures of active and passive smoking."

(n) Pershagen et al. - Passive Smoking and Lung Cancer in Swedish Women .

Although this article was received for publication in January 1986 it was not published until 1987, when it appeared in the American Journal of Epidemiology. The abstract reads as follows:

"The relation between passive smoking and lung cancer was examined by means of a case-control study in a cohort of 27,409 non-smoking Swedish women identified from questionnaires mailed in 1961 and 1963. A total of 77 cases of primary carcinoma of the bronchus or lung were found in a follow-up of the cohort through 1980. A new questionnaire in 1984 provided information on smoking by study subjects and their spouses as well as on potential confounding factors. The study revealed a relative risk of 3.3, constituting a statistically significant increase ($p < 0.05$) for squamous cell and small cell carcinomas in women married to smokers and a positive dose-response relation. No consistent effect could be seen for other histologic types, indicating that passive smoking is related primarily to those forms of lung cancer which show the highest relative risks in smokers."

The authors reported at p.20 that:

"Pooling the control groups produces a relative risk of 3.3 for squamous cell and small cell carcinomas (95 per cent confidence interval (CI) = 1.1-11.4) associated with marriage to a smoker. Within this group, the relative risks were increased for both histologic types. The relative risks for the other histologic types and for the entire group are 0.8 (95 per cent CI = 0.4-1.5) and 1.2 (95 per cent CI = 0.7-2.1) respectively."

202155070?

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Under the heading "Discussion" the authors stated the following:

> *"The results of our study indicate that exposure to environmental tobacco smoke is related to an increased risk of those histologic types of lung cancer which show the highest relative risks in smokers. This is in general agreement with the findings of Trichopoulos et al., Garfinkel et al, and Koo et al, although these authors looked at somewhat different carcinoma types and/or used other definitions of exposure."*
>
> (p.22)

(iii) The major reviews

I shall now refer to some of the more significant passages in the major reviews.

(a) The Monograph on Tobacco Smoking issued by the International Agency for Research on Cancer.

The International Agency for Research on Cancer ("IARC") is part of the World Health Organisation. This monograph ("the IARC report") represents the views and opinions of an IARC working group on the evaluation of the carcinogenic risk of chemicals to humans. The group met in Lyons from 12-20 February 1985. The report was published in June 1986. The report is part of a monograph programme the objective of which is to elaborate and publish in the form of monographs, critical reviews of data on, inter alia, carcinogenicity for chemicals to which humans are known to be exposed, to evaluate the data in terms of human risk with the help of international working groups of experts, and to indicate where additional research efforts are needed.

In the report the term "carcinogenic risk" is taken to mean the probability that exposure to the chemical will lead to cancer in humans. Inclusion of

2021550708

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

a chemical in the report does not imply that it is a carcinogen, only that the published data have been examined. The 28 members of the IARC working group were drawn from a variety of academic, medical research and other institutions in Europe, Asia, the Americas and Australia.

The manner in which IARC monographs are prepared is described in the report as follows. In advance of a meeting of a working group all relevant biological data concerning the substance under examination are collected by IARC. Six months before the meeting, articles containing relevant biological data are sent to experts, or are used by IARC staff, to prepare first drafts of the sections on biological effects. The complete drafts are then compiled by IARC staff and sent, prior to the meeting, to all participants in the working group for their comments. The working group meets to discuss and finalise the text of the monographs and to formulate the evaluations.

According to the report, the evidence for carcinogenicity from studies in humans is assessed by the working group and judged to fall into one of four groups, defined as follows:

> "*(i) Sufficient evidence of carcinogenicity indicates that there is a causal relationship between the exposure and human cancer.*
>
> *(ii) Limited evidence of carcinogenicity indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded.*

2021550709

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

(ii) *Inadequate evidence of carcinogenicity, which applies to both positive and negative evidence, indicates that one of two conditions prevailed:*

(a) there are few pertinent data; or

(b) the available studies, whilst showing evidence of association, do not exclude chance, bias or confounding.

(iv) No evidence of carcinogenicity applies when several adequate studies are available which do not show evidence of carcinogenicity."

(p.24)

The final evaluations of the IARC working group appear at the end of the report and include the following:

"There is sufficient evidence that tobacco smoke is carcinogenic to humans."

(p. 314)

Whilst the reference to tobacco smoke in this evaluation is not entirely free from ambiguity, in my opinion it is a reference to tobacco smoke from three sources, viz., mainstream smoke, sidestream smoke and smoke exhaled to the general atmosphere by smokers.

The bulk of the report is concerned with the effects of tobacco smoke on active smokers. In relation to passive smoking it contains the following observation:

"Several epidemiological studies have reported an increased risk of lung cancer in nonsmoking spouses of smokers, although some others have not. In some studies, the risk of lung cancer in nonsmokers increased in relation to the extent of spouses' smoking. Each of the studies had to contend with substantial difficulties in determination of passive exposure to tobacco smoke and to other possible risk factors for the various cancers studied. The resulting errors could arguably have artefactually depressed or raised estimated risks, and, as a consequence, each is compatible either with an increase or with an absence of risk. As the estimated relative risks are low, the acquisition of further evidence bearing on the issue may require large-

2021550710

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

scale observational studies involving reliable measures of exposure both in childhood and in adult life."

(p.308)

In a section headed "Conclusions and Evaluations", the following appears:

"Tobacco smoke affects not only people who smoke but also people who are exposed to the combustion products of other people's tobacco. The effects produced are not necessarily the same, as the constituents of smoke vary according to its source. Three main sources exist: (i) mainstream smoke, (ii) sidestream smoke, and (iii) smoke exhaled to the general atmosphere by smokers. Smokers are exposed to all three to a greater extent than are nonsmokers. It follows that it is unlikely that any effects will be produced in passive smokers that are not produced to a greater extent in smokers and that types of effects that are not seen in smokers will not be seen in passive smokers. Examination of smoke from the different sources shows that all three types contain chemicals that are both carcinogenic and mutagenic. The amounts absorbed by passive smokers are, however, small, and effects are unlikely to be detectable unless exposure is substantial and very large numbers of people are observed. The observations on nonsmokers that have been made so far are compatible with either an increased risk from 'passive' smoking or an absence of risk. Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during 'passive' smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens, however, leads to the conclusion that passive smoking gives rise to some risk of cancer."

(p.314)

(b) <u>The National Health and Medical Research Council report on Effect of Passive Smoking on Health</u>

Some time prior to June 1986 the Australian National Health and Medical Research Council set up a working party on the effects of passive smoking on health. The Chairman was Dr A.J. McMichael who, at the time, was Senior Principal Research Scientist, CSIRO Division of Human Nutrition. The other members of the working party were:

2021550711

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Dr R. Antic, Director of Thoracic Medicine, Royal Adelaide Hospital,
Dr C. Baker, Acting Executive Director of the Public Health Service of South Australian Health Commission,
Professor L. Landau, of the Department of Child Health at Princess Margaret Hospital for Children, Perth,
Professor S.R. Leeder, Head of the Department of Community Medicine, Westmead Hospital, Westmead,
Dr J.D. Potter, Senior Research Scientist at the CSIRO Division of Human Nutrition,
Dr A. Woodward, Lecturer in the Department of Community Medicine, Royal Adelaide Hospital, and
Dr. A.F. Dick, of the Health Care Committee of the Commonwealth Department of Health.

The report of the working party was adopted by the National Health and Medical Research Council in June 1986.

Chapter 7 of the report deals with passive smoking and cancer. The following quotations from the report do not include a number of footnotes in which reference is made to the published work of other scientists:

"*7.1 Introduction*

Tobacco smoke contains approximately sixty known or suspected carcinogenic chemicals, of which at least fifty occur in the phase that contains particulate matter. The carcinogenic activity of tobacco smoke appears to require this particulate phase. Animal bioassays indicate that sidestream tobacco tar is more carcinogenic per unit weight than mainstream tar. For public health purposes, therefore, it would be prudent to assume, at this stage of research activity, that mainstream and sidestream smoke have similar human carcinogenic potency.

There is no disagreement about the biological plausibility of an association between passive smoking and lung cancer. Active smoking is the major known cause of lung cancer, and there is a well-established monotonic increase in risk with increasing dose-rate. Further, no 'safe level' threshold dose appears to exist. Thus, although the dose rate for passive smokers is, overall, substantially lower than for active smokers, it is a reasonable inference from the studies of active smokers that passive smokers experience a real, albeit smaller, increase in lung cancer risk.

2021550712

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Nevertheless, it remains unknown how active and passive smoking might differ in terms of actual carcinogens delivered to the respiratory tract. Sidestream smoke is qualitatively richer in many smoke constituents than is mainstream smoke.

An equivalent argument exists in relation to the plausibility of passive smoking as a cause of cancers of other sites known to be related to active smoking.

7.2 Types of Epidemiological Evidence

There are two types of evidence by which to examine the relationship of passive smoking to cancer risk.

First, with knowledge of the established cancer risks of active smoking, and using the documented relationship between individual smoking behaviour and various biological indices of absorbed constituents of smoke (e.g. measures of nicotine and cotinine in blood and urine, thiocyanate and cotinine in saliva, and carboxyhaemoglobin in blood) to make direct estimations of the extent of non-smokers' exposure to smoke, it is possible to estimate the attendant risk of cancer. This approach presumes that the particular biological indices used are also indices of the carcinogenic potential of the inhaled and absorbed smoke. As indicated in Section 4, estimates based on biological measures indicate that passive smoking in the workplace typically entails exposures (for eight hours per day) equivalent to light active smoking. Light smokers are at approximately five times higher risk of lung cancer than non-smokers.

The second, and more usual, type of epidemiological evidence depends upon observing empirical associations between reported individual smoking habits and the occurrence of cancer. Such observations are made in either cohort (prospective) studies or case-control (retrospective) studies.

During 1979-85, eleven epidemiological studies examining the association between passive smoking and lung cancer have been reported. Most show a positive association, albeit substantially less strong than that between active smoking and lung cancer. Among non-smokers, the relative risk of lung cancer in passively exposed versus unexposed persons varies from approximately 1.2 to 3.5. A dose-response relationship is present in four of nine studies that have reported such an analysis. One cohort study has examined and reported the change in lung cancer risk associated with cessation of exposure (i.e. spouse as ex-smoker); a reduction in risk occurred.

During the same period, four epidemiological studies of passive smoking and non-lung cancers have been reported. Their findings have been less consistent than those pertaining to lung cancer.

2021550713

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

These variable results reflect not only the apparently smaller effect of passive smoking upon cancer risk than that of active smoking, but the associated small numbers of cases available for study, and the deficiencies in the validity and precision of measurement of individual exposure to passive smoking. Not only might some of the individuals included as non-smokers be ex-smokers, but the actual determination of exposure dosage - from varied sources and across time - is intrinsically difficult. Further, for the 25-50 per cent of women and the great majority of men in Western populations who work outside the home, the spouse's smoking habit is a poor quantitative index of passive smoking exposure - particularly since the exposure concentration is estimated to be four times higher at work than in the home. Nevertheless, to the extent that exposure misclassification applies equally to all combined groups of study subjects, it may have led to underestimation of the relative risk associated with passive smoking."

The report makes the following observations:

"The evidence that passive smoking causes lung cancer is strongly suggestive. It is plausible, moderately consistent, and demonstrates dose-response relationships. However, intrinsic difficulties in accurately classifying individual exposure, and insufficient numbers of study subjects in many studies, preclude a conclusive interpretation of these empirical data when considered in isolation from other corroborative scientific evidence."

The report concludes with the following quotation from a report of the interdisciplinary working group of the International Agency for Research in Cancer:

"'Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive" smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens, ... leads to the conclusion that passive smoking gives rise to some risk of cancer'."

Chapter 7 of the NH & MRC report is a statement of the findings of the working party. The Statement and Recommendations of the National Health & Medical Research Council itself are in Chapter 9 of the report, which reads, in part, as follows:

2021550714

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

"Council notes that there is mounting epidemiological evidence that passive smoking may increase the risk of occurrence of lung cancer. Despite limitations in the amount of data available, and despite research difficulties in making satisfactory estimations of individual exposure, a consistent pattern of moderately increased risk of lung cancer in passive smokers has emerged. In view of this pattern, of the known and substantial increase in risk of lung cancer in active smokers (and the lack of threshold dose), and of the documented levels of bodily assimilation of passively-inhaled smoke, it is therefore prudent public health policy to infer an increased risk of lung cancer from passive smoking."

(c) The 1986 report of the United States Surgeon General

In 1986 the United States Surgeon General issued a report entitled "The Health Consequences of Involuntary Smoking". The report was submitted to Congress on December 15, 1986. The report was prepared by the United States Department of Health and Human Services. The report lists the names of a number of individuals who prepared portions of the report. These persons hold positions in American universities. Acknowledgment is also given in the report to the assistance of about fifty scientists and physicians. It will be convenient to refer to this report as the "Surgeon General's 1986 Report".

The content of the report reflects the contributions of over sixty scientists representing a variety of disciplines. The care with which the report was apparently prepared appears from the Introduction:

"Upon receipt of the final manuscripts from the authors, the Office and its consultants edited and consolidated the individual manuscripts into appropriate chapters. These draft chapters were subjected to an extensive outside peer review ... whereby each was reviewed by up to several experts. Their comments were integrated and the entire volume was assembled. This revised edition of the Report was resubjected to review by 17 distinguished scientists outside the Federal Government, both in this country and abroad. Parallel to this review, the entire Report was also submitted to various

2021550715

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

institutes and agencies within the U.S. Public Health Service for review and comment."

The Introduction contains an overview of the report. After referring to the inhalation of tobacco smoke during active cigarette smoking as "the largest single preventable cause of death and disability for the U.S. population", the overview continues:

"The magnitude of the disease risks for active smokers secondary to their 'high dose' exposure to tobacco smoke suggests that the 'lower dose' exposure to tobacco smoke received by involuntary smokers may also have risks. Although the risks of involuntary smoking are smaller than the risks of active smoking, the number of individuals injured by involuntary smoking is large both in absolute terms and in comparison with the number injured by some other agents in the general environment that are regulated to curtail their potential to cause human illness.

This Report reviews the evidence on the characteristics of mainstream tobacco smoke and of environmental tobacco smoke, on the levels of exposure to environmental tobacco smoke that occur, and on the health effects of involuntary exposure to tobacco smoke. The composition of the tobacco smoke inhaled by active smokers and by involuntary smokers is examined for similarities and differences, and the concentrations to tobacco smoke components that can be measured in a variety of settings are explored, as is smoke deposition and absorption in the respiratory tract. The studies that describe the risks of environmental tobacco smoke exposure for humans are carefully reviewed for their findings and their validity. The evidence on the health effects of involuntary smoking is reviewed for biologic plausibility, and compared with extrapolations of the risks of active smoking to the lower dose of exposure to tobacco smoke found in nonsmokers. This review leads to three major conclusions:

1. *Involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers.*

2. *The children of parents who smoke compared with the children of nonsmoking parents have an increased frequency of respiratory infections, increased respiratory symptoms, and slightly smaller rates of increase in lung function as the lung matures.*

2021550716

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

3. *The simple separation of smokers and nonsmokers within the same air space may reduce, but does not eliminate, the exposure of nonsmokers to environmental tobacco smoke."*

The second conclusion does not, of course, relate to lung cancer.

The following statements are made in the report in relation to lung cancer:

"Exposure to environmental tobacco smoke has been examined in numerous recent epidemiological studies as a risk factor for lung cancer in nonsmokers. These studies have compared the risks for subjects exposed to ETS at home or at work with the risks for people not reported to be exposed in these environments. Because exposure to ETS is an almost universal experience in the more developed countries, these studies involve comparison of more exposed and less exposed people rather than comparison of exposed and unexposed people. Thus, the studies are inherently conservative in assessing the consequences of exposure to ETS. Interpretation of these studies must consider the extent to which populations with different ETS exposures have been identified, the gradient in ETS exposure from the lower exposure to the higher exposure groups, and the magnitude of the increased lung cancer risk that results from the gradient in ETS exposure.

To date, questionnaires have been used to classify ETS exposure. Quantification of exposure by questionnaire, particularly lifetime exposure, is difficult and has not been validated. However, spousal and parental smoking status identify individuals with different levels of exposure to ETS. Therefore, investigation has focused on the children and nonsmoking spouses of smokers, groups for whom greater ETS exposure would be expected and for whom increased nicotine absorption has been documented relative to the children and nonsmoking spouses of nonsmokers.

Of the epidemiologic studies reviewed in this Report that have examined the question of involuntary smoking's association with lung cancer, most (11 of 13) have shown a positive association with exposure, and in 6 the association reached statistical significance. Given the difficulty in identifying groups with differing ETS exposures, the low-dose range of exposure examined, and the small numbers of subjects in some series, it is not surprising that some studies have found no association and that in others the association did not reach a conventional level of statistical significance. The question is not whether cigarette smoke can cause lung cancer; that question has been answered unequivocally by

2021550717

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

examining the evidence for active smoking. The question is, rather, can tobacco smoke at a lower dose and through a different mode of exposure cause lung cancer in nonsmokers? The answer must be sought in the coherence and trends of the epidemiologic evidence available on this low-dose exposure to a known human carcinogen. In general, those studies with larger population sizes, more carefully validated diagnosis of lung cancer, and more careful assessment of ETS exposure status have shown statistically significant associations. A number of these studies have demonstrated a dose-response relationship between the level of ETS exposure and lung cancer risk. By using data on nicotine absorption by the nonsmoker, the nonsmoker's risk of developing lung cancer observed in human epidemiologic studies can be compared with the level of risk expected from an extrapolation of the dose-response data for the active smoker. This extrapolation yields estimates of an expected lung cancer risk that approximate the observed lung cancer risk in epidemiologic studies of involuntary smoking.

Cigarette smoke is well established as a human carcinogen. The chemical composition of ETS is qualitatively similar to mainstream smoke and sidestream smoke and also acts as a carcinogen in bioassay systems. For many nonsmokers, the quantitative exposure to ETS is large enough to expect an increased risk of lung cancer to occur, and epidemiologic studies have demonstrated an increased lung cancer risk with involuntary smoking. In examining a low-dose exposure to a known carcinogen, it is rare to have such an abundance of evidence on which to make a judgment, and given this abundance of evidence, a clear judgment can now be made: exposure to ETS is a cause of lung cancer.

The data presented in this Report establish that a substantial number of the lung cancer deaths that occur among nonsmokers can be attributed to involuntary smoking. However, better data on the extent and variability of ETS exposure are needed to estimate the number of deaths with confidence."

After making extensive reference to the scientific literature as to the relationship between passive smoking and lung cancer the Surgeon General's Report adopts the following summary:

"Previous Reports of the Surgeon General have reviewed the data establishing active cigarette smoking as the major cause of lung cancer. The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream smoke and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk

2021550718

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

in some populations with exposures to ETS leads to the conclusion that involuntary smoking is a cause of lung cancer."

"The epidemiological evidence that involuntary smoking can significantly increase the risk of lung cancer in nonsmokers is compelling when considered as an examination of low-dose exposure to a known carcinogen (i.e., tobacco smoke). Eleven of the thirteen epidemiological studies to date show a modest (10 to 300 percent) elevation of the risk of lung cancer among nonsmokers exposed to involuntary smoking; in six studies positive associations were statistically significant. The studies showing no or non significantly positive findings were generally the weakest in terms of sample size (Gillis et al. 1984; Chan and Fung 1982; Koo et al. 1984; Kabat and Wynder 1984; Wu et al. 1985; Lee et al. 1986), study design (Kabat and Wynder 1984; Lee et al. 1986), or quality of data (Chan and Fung 1982)."

After detailed reference to the epidemiological studies referred to in the report, the summary concludes:

"The magnitude of risk associated with involuntary smoking exposure is uncertain. Relative risks ranging from 2 to 3 were generally reported for the highest level of exposure based on the spouses' smoking habits, but since sample sizes in most studies are not large, the point estimates of effect are unstable, and confidence limits are broad and generally overlap from one study to another. An index of involuntary smoking based on the smoking habits of the spouse is a simplistic and convenient measure. There is no reason to believe, however, that the excess risk associated with involuntary smoking is restricted to exposure from spouses. Nonsmokers married to smokers are likely to be more tolerant of ETS exposure and to experience more exposure to environmental tobacco smoke (Wald and Ritchie 1984). Higher risk estimates for involuntary smoking have been obtained in studies restricted to squamous cell and small cell carcinomas of the lung.

Although involuntary smoking can be established as a cause of lung cancer, important questions related to this exposure require further research. More accurate estimates for the assessment of exposure in the home, workplace, and other environments are needed. Studies of sufficiently large populations should also be performed. New data from such studies should yield more certain risk estimates and describe the magnitude of the lung cancer risk in nonsmokers."

The following statements appear in the report:

2021550719

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

"The appropriate framework for an examination of the lung cancer risk from involuntary smoking is that of a low-dose exposure to a known human carcinogen. Over 30 years of research have conclusively established cigarette smoke as a carcinogen. This Report presents evidence that the chemical composition of sidestream smoke is qualitatively similar to the mainstream smoke inhaled by the active smoker, and that both mainstream and sidestream smoke act as carcinogens in bioassay systems. Data related to environmental levels of tobacco smoke constituents and from measures of nicotine absorption in nonsmokers suggest that nonsmokers are exposed to levels of environmental tobacco smoke that would be expected to generate a lung cancer risk; epidemiological studies of populations exposed to ETS have documented an increased risk for lung cancer in those nonsmokers with increased exposure.

It is rare to have such detailed exposure data or human epidemiologic studies on disease occurrence when attempting to evaluate the risk of low-dose exposure to an agent with established toxicity at higher levels of exposure. The relative abundance of data reviewed in this Report, their cohesiveness, and their biologic plausibility allow a judgment that involuntary smoking can cause lung cancer in nonsmokers. Although the number of lung cancers due to involuntary smoking is smaller than that due to active smoking, it still represents a number sufficiently large to generate substantial public health concern.

It is certain that a substantial proportion of the lung cancers that occur in nonsmokers are due to ETS exposure; however, more complete data on the dose and variability of smoke exposure in the nonsmoking U.S. population will be needed before a quantitative estimate of the number of such cancers can be made."

(d) <u>The National Research Council report on Environmental Tobacco Smoke 1986</u>

The National Research Council is the principal operating agency of the National Academy of Sciences of the United States of America. It was requested by the United States Department of Health and Human Services to evaluate methods for assessing exposure to environmental tobacco smoke and to review the literature on the health consequences of such exposure. The Council responded to this request by appointing eleven scientists to serve on a committee. The committee's charge was to review the then existing scientific literature and to identify the then current state of

2021550720

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

knowledge with respect to known facts and areas of uncertainty. (Ex D3,p.v). The committee membership represented the disciplines of toxicology, biochemistry, atmospheric science, epidemiology, bio-statistics and pulmonary physiology. For the most part, the members of the committee were drawn from American universities (including Harvard, Yale and Johns Hopkins), but its members also included Professor Nicholas Wald, Professor of Environmental and Preventative Medicine at St Bartholomew's Hospital, London, as well as Olav Axelson of the University Hospital, Linkoping, Sweden. According to its report, the committee conducted a public hearing on scientific studies relevant to its charge and reviewed the published scientific literature and received testimony from professional societies; medical, industry, consumer and public interest groups, academic scientists; and other involved in the generation and interpretation of scientific evidence on the health consequences of exposure to cigarette smoking. The public hearing was held on January 29, 1986. The report is undated but was first printed in November 1986. I think it is a reasonable inference that the material upon which the report was based was available to the scientific community as at July 1986. It will be convenient to refer to this report as "the NRC report".

With respect to lung cancer the report (pp.10-11) makes the following statement:

> *"Considering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers. Estimates of the magnitude of the increased risk vary. Among studies of various populations in Europe, Asia and North America, the risk of lung cancer is roughly 30% higher for nonsmoking spouses of smokers than it is for nonsmoking spouses of nonsmokers. There is consistency among the studies in that all of the studies individually include the 30% increased risk within the 95%*

2021550721

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

confidence intervals. Patterns and extent of exposure may vary in different communities and countries. Based on presently available epidemiologic data, the estimate of the increased risk from the American studies is lower than the average for all the studies, though not significantly so. These estimates are almost exclusively derived from the comparison of persons identified as exposed, or unexposed, on the basis of their spouse's smoking habits.

Certain errors in the reporting of smoking habits have probably contributed to the risks observed in the epidemiologic studies. Misclassification of current or exsmokers as nonsmokers would tend to produce an observed relative risk that is larger than the true risk. The effect was studied in detail using estimates of the extent of the errors involved and judged to contribute only a portion of the excess risk. Underestimation of the increased risk might also be introduced because the supposedly unexposed population had some exposure to ETS, although they were classified as unexposed in the studies. Taking both types of errors into account produces an estimate of the excess lung cancer risk for nonsmokers married to smokers compared with completely unexposed individuals that is similar to the relative risk observed in the epidemiologic studies considered.

Since carcinogenic agents contained in ETS are inhaled by nonsmokers, in the absence of a threshold for carcinogenic effects, an increased risk of lung cancer due to ETS exposure is biologically plausible."

Chapter 12 of the report is entitled "Exposure to Environmental Tobacco Smoke and Lung Cancer". After observing that the risk of lung cancer in cigarette smokers is directly related to the number of cigarettes smoked and that, among smokers, an increase in exposure leads to an increase in risk, the authors state that passive smoking would, therefore, be expected to cause some increase in risk of lung cancer in active smokers, as well as in any other persons in whom the appropriate tissues are exposed. They continue:

"The studies reviewed in this chapter have attempted to address the questions of whether an increase in risk of lung cancer does occur in nonsmokers exposed to ETS and whether the dose-response relationship is similar to that in smokers. In part, this depends on whether there is a threshold dose of cigarette smoke exposure below which there is no

2021550722

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

increase in risk. Biological theory and current evidence on low-dose exposure to carcinogens do not provide evidence for such a threshold, and it is generally thought that one is unlikely (Office of Science and Technology Policy, 1985). If there is no threshold, it follows that exposure to tobacco smoke at low concentrations, such as that experienced by nonsmokers exposed to ETS, will cause an increased risk of lung cancer. The risk, of course, will be expected to be very much smaller than that associated with active smoking because of the much lower exposure of the bronchial epithelium to tobacco smoke."

After a detailed examination of the scientific literature on the subject and a consideration of bias and misclassification factors which may have affected some or all of the studies reported in the literature, the following summary is made:

"The weight of evidence derived from epidemiologic studies shows an association between ETS exposure of nonsmokers and lung cancer that, taken as a whole, is unlikely to be due to chance or systematic bias. The observed estimate of increased risk is 34%, largely for spouses of smokers compared with spouses of nonsmokers. One must consider the alternative explanations that this excess either reflects bias inherent in most of the studies or that it represents a causal effect. Misclassification can have contributed to the result to some extent. Computations of the effect of two sources of misclassification were presented. Computations taking into account the possible effects of misclassified exsmokers and the tendency for spouses to have similar smoking habits placed the best estimate of increased risk of lung cancer at about 25% in persons exposed to ETS at a level typical of that experienced by nonsmokers married to smokers compared with those married to nonsmokers. Another computation using information from cotinine levels observed in nonsmokers and taking into account the effect of making comparisons with a reference population that is truly unexposed leads to an estimated increased risk of about one-third when exposed spouses were compared with a truly unexposed population. The finding of such an increased risk is biologically plausible, because nonsmokers inhale other people's smoke and, as a result, absorb smoke components containing carcinogens.

What is Known

1. A summary estimate from epidemiologic studies places the increased risk of lung cancer in nonsmokers married to smokers compared with nonsmokers married to nonsmokers at about 34%. Assuming linearity at low-to-average doses and a constant proportionality of nicotine and carcinogens in mainstream smoke and ETS, extrapolation from

2021550723

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

studies of active smokers using relative urinary cotinine places the risk at about 10%.

2. To some extent, misclassification (bias) may have contributed to the results reported in the epidemiologic literature. However, bias is not likely to account for all of the increased risk. The best estimate, allowing for reasonable misclassification, is that the adjusted risk of lung cancer is increased about 25% (i.e., RR = 1.25) in nonsmokers married to smokers compared with nonsmokers married to nonsmokers. When one allows for exposure to nonsmokers who report themselves as unexposed, the adjusted increased risk is at least 24%. The adjusted increased risk to a group of nonsmokers married to nonsmokers is at least 8% (i.e., RR = 1.08) compared with truly unexposed subjects. This excess risk may come about from exposures in the workplace or other public places."

(e) The Froggatt Committee report 1988

This report was made in January 1988 by the Independent Scientific Committee on Smoking & Health to the Secretary of State for Social Services (UK). According to the Committee's Report its responsibility is "to advise ... on scientific aspects of matters concerning smoking and health ...".

Chapter 3 of the report addresses questions related to the effect of exposure to ETS. In the following quotations from the report I have omitted footnotes which contain references to scientific literature:

"64. Nicotine is virtually unique to tobacco and might be considered therefore as an index of ETS. Its uptake by non-smokers, as measured by its metabolites, indicates that some passive smokers may receive a dose equivalent to that received by smokers who smoke a small number of cigarettes. However, since sidestream and mainstream smoke differ in composition such measurements cannot be extrapolated to the whole range of potentially harmful constituents of the smoke. For example, when dimethylnitrosamine rather than nicotine is used as a marker, the estimation of the uptake of tobacco smoke produces a greater equivalence. Recent work has also pointed to the role that ETS can play in enhancing concentrations of radon daughter products indoors. For these, and other reasons it is unwise to express ETS uptake in terms of an equivalent

2021550724

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

number of cigarettes actively smoked despite its undoubted convenience, a point made in our interim report in March 1987.

65. The mutagenicity of particulate material sampled from indoor and outdoor air has been studied using bacterial systems and smoking was found to be an important factor with its predominant effect on enzyme mediated mutagenesis, the number of revertants increasing with the number of cigarettes smoked.

66. Attempts have been made to evaluate relative risk by means of epidemiological studies, not surprising given the hypothesis of a zero threshold and that non-smokers absorb some of the carcinogenic agents produced in smoking, though the exact proportion is unknown. The commonest method is to investigate lung cancer incidence among non-smoking wives of husbands who are, or are not, smokers. Studies of adequate size with documented smoking histories of cases and spouses are few and our review has therefore covered surveys from many countries.

67. In our Third Report we concluded (para 35) that the reported association between passive smoking and lung cancer was speculative. Since then a number of new studies have been reported. The majority of reports conclude that passive smoking is associated with an increased risk of lung cancer in non-smokers. A minority conclude from their own data that any effect of passive smoking on the risk of lung cancer or other smoking-related disease in a non-smoker is negligible and that the increased risk noted in other studies is largely an artefact.

68. The published studies have been scrutinized by various groups of researchers to determine whether collectively they present a reasonably consistent picture from which the existence and magnitude of the relative risk might be assessed. The major problem is the extent to which individuals with lung cancer were misclassified as non-smokers when they were in fact smokers or ex-smokers. After making allowances for such misclassifications, and other artifacts, and then recalculating relative risks in each study, most of the scientific groups conclude that while none of the studies can on its own be accepted as unequivocal the findings overall are consistent with there being a small increase in the risk of lung cancer from exposure to environmental tobacco smoke, in the range 10 per cent-30 per cent, though some other workers have however argued for a much lower relative risk, or no increased risk at all. The Committee, studying the same data, agrees with the former interpretation and so upholds the view expressed in its interim statement.

69. It is helpful to state exactly what is meant by a 10% to 30% increased risk. It means that people who have never smoked but who have been exposed to environmental tobacco smoke through most of their lives have a 10% to 30% higher risk of lung cancer than non-smokers not so exposed. If the risk in the latter group is, say, 10 per 100,000 per year

2021550725

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

(based on rates in non-smokers in the 35+ age range) the risk in the exposed group would be 11 to 13 per 100,000 per year. Thus there might be 1 to 3 extra lung cancer cases a year per 100,000 non-smokers regularly exposed to ETS. Since there are no firm data on the numbers of people who fall into that category, no more than a rough estimate of the actual number of lung cancer deaths arising in this way could be made. It might however amounts to several hundred out of the current annual total of about 40,000 lung cancer deaths in the United Kingdom, a small but not negligible proportion. In view of this conclusion we recommend that -
FURTHER PUBLICITY SHOULD BE GIVEN TO THE RISK OF LUNG CANCER ARISING FROM EXPOSURE TO OTHER PEOPLE'S TOBACCO SMOKE"

(iv) Oral evidence

I shall now refer to some of the oral evidence as to the alleged association between passive smoking and cancer.

(a) Professor Stewart

Professor Bernard Stewart is Associate Professor in the School of Paediatrics at the University of New South Wales, and is the Principal Research Fellow in the Children's Leukaemia and Cancer Research Unit at the Prince of Wales Children's Hospital. He is a bio-chemist with specialist experience in the field of carcinogenesis. For a number of years he was the senior Research Fellow in Carcinogenesis of the New South Wales State Cancer Council.

Professor Stewart has had a great deal of experience in the study of the carcinogenic qualities of tobacco smoke. He expressed the opinion that there was no doubt whatever that cigarette smoke had been shown "to the point of absolute certainty" to be carcinogenic for humans (T. 433). In his opinion, exposure for a short

2021550726

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

time t) a high concentration of tobacco smoke is less dangerous to humans than exposure to a low concentration of smoke over a long period of time. The reason for this is that if exposure occurs over a long period of time the likelihood of malignancy is increased because cells tend to be pushed towards transformation or alteration i.e. to become cancerous, rather than being killed outright. According to Professor Stewart, there is no safe level of exposure to carcinogenic substances, whereas the same cannot be said of toxic substances. A chemical is carcinogenic if it has the capacity to cause normal cells to become malignant. Toxic chemicals are those which kill normal cells (T. 396). Carcinogenic chemicals may also have a toxic effect.

Professor Stewart explained his view that there is no safe level of exposure to carcinogens, as distinct from toxins, in the following words:

> *"For the vast majority of toxins, for the vast majority of chemicals that adversely [affect] us as people, the adversity that the chemicals produce is related to the dose. If the dose is large then obviously the toxic chemical will cause death - or large enough. As the dose is reduced so the extent of pathology produced by that chemical is reduced and if the dose is reduced and reduced there comes a point where there is no discernible toxic effect at all. So that, for argument's sake, in respect of caustic soda. Although caustic soda is toxic, it will be possible to take a solution of caustic soda and dilute and dilute it until it was so diluted as to be consumed without causing any clinical injury to the oesophagus. Now that concept is [basic] to public health insofar as when measures to protect the community from toxins are taken, the concept of a safe level of exposure is crucial. That concept can be clearly distinguished from the same basis when one approaches carcinogenic hazards because carcinogenicity is not so related to dose. At two levels because the theory of carcinogenesis says that a single cell to be modified and give rise to a tumour in theory such a single modification could produce a lethal response. If you poison a cell in the oesophagus with caustic soda the death of one cell could not possibly cause the death of the whole person but if you produce a single malignant cell then in theory that cell can grow into a tumour and produce the death of the individual. So that is a conceptual basis for the idea that there is no safe dose for a known carcinogen. The other aspect of that concept is based on the investigation of that whole area. That is in addition to the*

2021550727

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

conceptual basis of that idea, no safe dose, there is a body of experimental evidence pertaining to either people or experimental animals that have been exposed to lower and lower levels of carcinogen by one reason or another and all of that data taken as a whole has failed to indicate a safe level of exposure for the carcinogen under review. So it is a [basic] tenet of carcinogenesis that there is no safe level of exposure, a principle that lies at the very heart of all other areas of toxicology."

(T.397-8)

It is apparent from statements made in the written material which I admitted into evidence that Professor Stewart's view that there is no safe level of exposure to a carcinogen is shared by many distinguished scientists.

It was put to Professor Stewart in cross-examination that if his view is correct, one molecule of a carcinogen could cause cancer. Whilst he agreed that, in theory, this was correct, he said that the one molecule example was a trivialisation of the significance of minimal exposure to carcinogens. I think this is correct, particularly in the context of the present case. The reference to cigarette smoke in the statement in para. 3 of the advertisement is quite general. It would extend, for example, to cigarette smoke inhaled by a non-smoker working for many years beside and in close proximity to a heavy smoker. If it be true that environmental tobacco smoke contains carcinogenic chemicals, it would be quite unrealistic to regard such a non-smoker as being exposed to the risk of inhaling only one molecule of a carcinogen.

Professor Stewart drew support for his opinions from the findings contained in some of the primary articles and also the findings in the IARC report. He conceded in one part of his evidence (T.521) that the available epidemiological

2021550728

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

evidence does not allow a judgment to be made on causality between lung cancer and exposure to environmental tobacco smoke. However, in the light of all his evidence, I did not understand this concession to be a concession that it has not been proved that cigarette smoke causes lung cancer in non-smokers. The concession he made was limited to the effect of the available epidemiological evidence, if considered in isolation from other evidence. It is plain from his evidence that he is firmly of the opinion that there is a considerable volume of evidence that cigarette smoke causes disease in non-smokers (T. 522). He thinks that exposure to tobacco smoke is an established carcinogenic hazard. According to him, this conclusion can be reached wholly on the basis of laboratory evidence without reference to the epidemiological studies. However, he thinks both types of evidence should be considered together. He said: "Complementarity of laboratory and epidemiological evidence, in respect of the carcinogenic hazard associated with exposure to environmental smoke is unequivocal. In view of these considerations, denial that evidence for a carcinogenic hazard from passive smoking has not been established, is absurd" (see annexure E to his affidavit).

A consideration of the whole of Professor Stewart's evidence leads me to conclude that he is of the opinion that a causal link has been established between passive smoking and lung cancer in non-smokers, but that further epidemiological evidence would add weight to his opinion. In his affidavit he said:

> *"In my opinion, understanding of the causation of lung cancer in cigarette smokers, taken together with knowledge of the nature of sidestream and mainstream tobacco smoke, of the materials absorbed during passive smoking and of the quantitative relationships between dose and effect that*

2021550729

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

are commonly observed after exposure to carcinogens, leads to the reasonable presumption that passive smoking does carry some risk for lung and other cancers. In respect of lung cancer, this presumption is now confirmed by a variety of epidemiological and experimental evidence which are mutually supportive. Knowledge of the causal relationship between passive smoking and lung cancer is now sufficient as to warrant measures to limit human exposure to this risk factor as a necessary and practicable public health measure to reduce the burden of lung cancer in the community."

Professor Stewart said that undiluted sidestream smoke is characterised by significantly higher concentrations of many of the toxic and carcinogenic compounds found in mainstream smoke. According to him, a comparison of the chemical composition of smoke inhaled by active smokers with that inhaled by involuntary smokers suggests that the toxic and carcinogenic effects would be qualitatively similar. He said that since carcinogenic agents in environmental tobacco smoke are inhaled by non-smokers, in the absence of a threshold for carcinogenic effects, an increased risk of lung cancer due to environmental tobacco smoke is anticipated.

Professor Stewart conceded that active smokers are exposed to greater quantities of tobacco smoke constituents than involuntary smokers. However, he is of the view that exposures to respirable suspended particulates are higher for non-smokers exposed to environmental tobacco smoke than for non-smokers who are not so exposed.

It was put to Professor Stewart in cross-examination that the proposition that there is no safe dose for a carcinogen was a public health principle and that public health principles depend upon dictates of caution whereas scientific proof of a

2021550730

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

prop osition depends on demonstration of its correctness (T. 491-2). The Professor agre d, but I do not think his agreement is tantamount to an admission that there is not cientific proof that there is no safe dose for a carcinogen. He specifically disag eed with the proposition put to him (T. 494) that the concept that there was no thres iold for carcinogens was not universally accepted. He said he knew of no expe imental studies that had satisfactorily demonstrated that there was any such thres iold (T. 494).

Professor Stewart said there was no qualitative distinction as to carci ogens between the composition of mainstream smoke and sidestream smoke beca se both contained polycyclic hydro carbons and both contained nitroso comp ounds or that group of nitroso compounds called nitrosamines (T.416). How ver, under cross-examination Professor Stewart conceded that it has not been scien fically proven that nitroso compounds cause cancer in humans (T.485). He said he b lieved there was a split within the scientific community on that issue. In his opini n nitroso compounds "would be appropriately characterized as a group 2A comp ound, that is they probably cause cancer in humans but it is not proven" (T. 4 5). Later, Professor Stewart elaborated:

> "... *whether nitroso compounds cause cancer in humans. Now, that statement is by definition concerned with the causation of cancer in humans and can only be resolved by reference to epidemiology studies in humans. The animal data are suggestive but not definitive and the reason I appear to equivocate on it is that the generally appropriate generalization is certainly that nitroso compounds probably cause cancer in humans or nitroso compounds almost certainly cause cancer in humans but my studies on rats and mice or on rats are not relevant to the definitive determination that nitroso compounds cause cancer in humans. They only provide evidence consistent with such a proposition or even evidence*

2021550731

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

that was strongly suggestive or almost leaving no room for doubt but they are not finally definitive ..."

(T.519-520).

I refer elsewhere to the contents of the IARC report and it is instructive to compare Professor Stewart's opinions with the conclusions reached in it. At p.314 of the report, after reference is made to the three main sources of tobacco smoke i.e. mainstream smoke, sidestream smoke, and smoke exhaled to the general atmosphere by smokers, it is said:

"Examination of smoke from the different sources shows that all three types contain chemicals that are both carcinogenic and mutagenic. The amounts absorbed by passive smokers are, however, small, and effects are unlikely to be detectable unless exposure is substantial and very large numbers of people are observed. The observations on nonsmokers that have been made so far are compatible with either an increased risk from 'passive' smoking or an absence of risk. Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during 'passive' smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens, however, leads to the conclusion that passive smoking gives rise to some risk of cancer."

The report then makes the evaluation that:

"There is sufficient evidence that tobacco smoke is carcinogenic to humans."

Reference to p.24 of the report shows that the expression "sufficient evidence" of carcinogenicity indicates that there is a causal relationship between the exposure and human cancer. Thus Professor Stewart's opinions seem not to differ from those expressed in the report.

2021550732

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

(b) **Professor McMichael**

Professor Anthony McMichael is Professor of Occupational and Environmental Health in the Department of Community Medicine at the University of Adelaide. He was the Chairman of the working party which produced the NH & MRC report. Prior to taking up his present appointment he was Senior Principal Research Scientist with the Commonwealth Scientific Industrial and Research Organisation. He was at one time Assistant Professor in the Department of Epidemiology in the University of North Carolina, U.S.A.

Professor McMichael is of the opinion that it is not true to say that there is little evidence that cigarette smoke causes disease in non-smokers. In his opinion, there is a considerable volume of evidence that cigarette smoke causes disease in non-smokers and the evidence is sufficient to constitute scientific proof that it does so.

Professor McMichael took a very active part in the preparation of the chapter in the NH & MRC report dealing with cancer. It is plain from his evidence that he shares the view expressed in the report. Indeed, with respect to the statement made on p.33 of the report that: "The evidence that passive smoking causes lung cancer is strongly suggestive" the Professor said that this was an understatement of the view which he himself held at the time.

The respondent sought to diminish the weight which should be given to Professor McMichael's evidence by showing that he had altered a draft report

2021550733

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

prepared for the consideration of the working party. I do not think it was shown that he did anything untoward in the handling of the draft report. Certainly he was responsible for the making of some alterations, but I am quite satisfied there was nothing improper in what he did. The members of the working party were all persons with high qualifications and great experience. I think it is reasonable to assume that they did not concur with Professor McMichael's views unless they shared his opinions as expressed in the final report.

Counsel for the respondent criticised Professor McMichael for showing a copy of the draft NH & MRC report to a body known as ASH, an acronym for Action on Smoking and Health. However, I can see nothing wrong with what he did in this regard. It is true that the draft was, at the time, a confidential document but as he pointed out there were many groups concerned with public health who knew of its existence, or at least knew that work was being done on the report. There is nothing to suggest that if the respondent had asked to see a copy of the draft report it would not have been shown it.

Professor McMichael's opinions have firmed since the publication in July 1986 of the NH & MRC report. He said (T. 969) that as at January 1987 his view was "a little firmer that there was a causal relationship demonstrated between passive smoking and lung cancer." It is apparent from his evidence that one reason why his opinion had firmed was the publication in late 1986 of an article by Professor Wald and others published in the British Medical Journal. Reference to this article,

2021550734

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

and to Professor Wald's evidence in respect of it, is made elsewhere in these reasons. Professor McMichael said he agreed with the conclusions in Wald's article.

It would not be right, however, to treat Professor McMichael's evidence as being merely an adoption and recapitulation of the views expressed by Wald and other writers of published scientific work. He made it plain that although he had regard to the views of others, he had arrived at his own opinions. Thus he said:

> *"I do not depend centrally on Wald because Wald has done simply quantitatively in a way that I consider to be correct and appropriate the sort of thing that otherwise one has done, one does mentally or qualitatively in appraising the full set of results available."*
>
> (T. 1347)

Professor McMichael's views are perhaps best captured in the following statements he made towards the conclusion of his evidence. The statements were made in the context of drawing a comparison between the evidence showing a link between the consumption of alcohol and breast cancer and the evidence showing a link between passive smoking and lung cancer. Although the statement is lengthy, I set it out in full because it encapsulates the gist of the arguments relied upon by the applicant on the question whether passive smoking causes lung cancer. He said (T. 1413-4):

> *"With respect to ... tobacco smoke in human cancer, ... I would summarize the evidence in relation to active smoking and here we are talking not about 5, 10 or 20 or even hundreds of studies, but in totality thousands of human and animal experimental studies as showing very consistent and strong increases in risk of human cancer, particularly, cancer of the lung in epidemiological research - that is work spread now over three or four decades. An enormous range of corroborative evidence from animal experiments with tobacco smoke being encountered in different modes, either by inhalation or painting on the skin. A lot of work on the*

2021550735

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

mutational capacity of cigarette smoke. Studies on the induction of genetic mutations in mammalian cells and in bacterial cells. With respect to the evidence on environmental tobacco smoke we have first up the epidemiological evidence, ... that is studies specifically of the risk of lung cancer in life-long non-smokers exposed to environmental tobacco smoke, so we have that direct empirical evidence, although we have noted that the number of studies is not great. It is moving towards a total of around 20 now and if we were looking at those just on their own, and if they had arisen out of the blue, as it were, as has been the case for alcohol and breast cancer or methylxanthenes and breast cancer, that had arisen recently out of the blue, not against a background of all of this other corroborative scientific work and all of this other biological knowledge and theory, then we would be more cautious in drawing a causal inference. But because there is the overwhelming evidence from the studies of active smoking because we have from the toxicologists and chemists the evidence of the qualitative identity in terms of chemical constituents present, of active and passive smoke ... we would reasonably infer that that exposure has a capacity to produce cancers. ... we have a range of metabolic epidemiological studies in which it has been demonstrated that humans exposed to environmental tobacco smoke, whether at home, at work or in some other context, public transport and so, by measuring levels of cotinine in blood, urine, saliva and so on, it has been clearly established that non-trivial amounts of exposure are incurred by those individuals and that that is in some quantitative proportion to the types of exposures that might be estimated by direct environmental observation or by asking individuals, how much does your husband smoke and how much is it at work, etcetera. So we ... not only ... have those initial upfront studies from epidemiologists about environmental tobacco smoke in lung cancer, but we have this extraordinarily rich large and deep spectrum of scientific research, some of it bearing directly on environmental tobacco smoke, much of it bearing on active tobacco smoke which provides the sort of corroboration that in my judgment allows one to draw a reasonable inference of causality from the sort of evidence that has now accrued in relation to environmental tobacco smoke."

Professor McMichael expressed the opinion that, qualitatively, environmental tobacco smoke and mainsteam smoke have much the same chemical constituency (T. 928). He accepted that there were important quantitative differences, one of which was that at the point of origin the concentration of a number of chemicals is actually greater in sidestream smoke than it is in mainstream smoke. He said these chemicals include several chemicals which are carcinogenic.

2021550736

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Professor McMichael also shares the views of other witnesses in the case, and a view expressed in much of the literature, that there is no apparent threshold for carcinogens, i.e. no apparent safe dose or level of exposure below which there is no increase in the risk of lung cancer from tobacco smoke (T.937).

The respondent sought to diminish the quality of some of the epidemiological studies referred to by Professor McMichael because the diagnosis of cancer in some of them depended upon cytological rather than histological examination. A histological examination involves taking a small piece of the tissue of the tumour of interest and examining it microscopically so as to form a judgment about its histology. Cytological examination involves taking specimen cells from the tumour and examining them microscopically. Professor McMichael accepted that histological examination provides a surer guide to a correct diagnosis than cytological examination, and that both are more reliable than diagnoses recorded on death certificates. There was no disagreement between the witnesses on this matter. However, in my opinion, the respondent's witnesses tended to place far too much emphasis on the absence of histological examination in some of the surveys.

Professor McMichael, in common with other witnesses, was cross examined at length as to much of the detail in the epidemiological studies relied upon by the applicant. It is impracticable to traverse in these reasons all of the ground covered in the cross examination. In his cross examination of the applicant's witnesses, Mr O'Keefe Q.C. was able to identify many aspects of the studies upon which they could be criticised. He was also able to show that, within some of the

2021550737

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

studies, there were apparent inconsistencies. But Professor McMichael would not accept that the studies could therefore be discarded. He said repeatedly that what was of importance from an epidemiological point of view was consistency in epidemiological studies. As he said:

> *"It is always very important to look for consistency of findings across studies. There is a sort of hybrid vigour, if you like, or robustness that derives from making similar observations in different population settings and using different study designs."*
>
> (T.923)

This approach is also reflected in his appreciation of the importance of statistical significance. Lack of statistical significance in data derived from a study was regarded on the respondent's side as of almost crucial importance. However, Professor McMichael's opinion is that it is inappropriate to regard statistical significance as the sole criterion of the value of an epidemiological study. He regards statistical significance as only one aid to judgment in deciding how much weight should be attached to a study.

In Professor McMichael's opinion, the value of an epidemiological study cannot be ascertained by measuring it against set criteria. He said (T. 1238) that whilst there are recognised and important criteria for the drawing of judgments about causal inference, they are not and should not be seen as pre-requisites to the drawing of such judgments. In his opinion, the drawing of causal inferences can quite reasonably proceed, and often does, in the presence of some only of the well recognised criteria.

2021550738

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Professor McMichael's view that it is the totality of all the evidence which is of importance can be seen from his view as to when a causal inference can be drawn. He said:

> *"[I] think we have to be aware again that we are talking about a continuum that moves from uncertainty to certainty in the drawing of these causal inferences, and that is not really a binary option that you either do or do not know that there is a causal relationship. It is very much a question of the accrual of evidence and the level of certainty that applies."*
>
> (T. 1253)

Professor McMichael said that taking into account the totality of the scientific evidence he was satisfied that, as at mid-1986, there was sufficient evidence to allow the drawing of an inference of causality between exposure to passive smoking and the occurrence of lung cancer in humans. (T. 1269). The above references to his evidence barely scratch the surface of it. I have not attempted to deal with the detailed evidence he gave, much of it in the course of cross examination, about the epidemiological studies referred to in the primary articles. Indeed, it would be almost impossible to capture in these reasons the intricacies of that evidence. However, I should observe that I formed the opinion that Professor McMichael is highly skilled in the field of cancer epidemiology and that his opinions are entitled to great respect.

.../72

2021550739

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

(c) Dr Armstrong

Dr Bruce Armstrong is Commissioner of Health for the State of Western Australia. Prior to that appointment he was Director of the National Health and Medical Research Council's Research Unit in Epidemiology and Preventative Medicine and Professor of Epidemiology and Cancer Research at the University of Western Australia.

Dr Armstrong is of the opinion that it is not true to say that there is little evidence that cigarette smoke causes disease in non-smokers. He thinks there is considerable scientific evidence that cigarette smoke causes disease in non-smokers and that the evidence is sufficient to prove this relationship on the balance of probabilities. In his opinion sidestream smoke is a rich source of toxic substances and contains a variety of known or suspected chemical carcinogens in amounts as much as thirty times higher than in mainstream smoke. (Annexure E to his affidavit). He is of the view that there is no theoretical or empirical reason to postulate a low-dose threshold for tobacco smoke carcinogenesis. He holds the opinion that the products of tobacco combustion are readily measurable and that their inhalation and absorption in the human body is demonstrable by the measurement of cotinine in the urine of non-smokers.

Dr Armstrong adheres to the view he expressed in an article which he published in 1987. In that article he said:

> *"Knowledge derived from studies of 'active' smokers, evidence of exposure to tobacco smoke carcinogens through passive smoking and the results of studies of passive smokers themselves are concordant in suggesting that*

2021550740

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

passive smoking gives rise to a small increase in the risk of lung cancer in non-smokers. The actual degree of increase in risk must, for the present, be considered as somewhat uncertain. Estimates of carcinogen exposure through passive smoking suggest that it may be as low as 14 per cent; studies of lung cancer itself suggest that it lies between 24 per cent and 61 per cent. Similar or perhaps greater absolute increases in risk of lung cancer due to passive smoking would be likely in current and ex-smokers but probably undetectable epidemiologically because of the associated high incidence of lung cancer due to active smoking."

I did not understand there to be any material difference between Dr Armstrong's views on matters relevant to this case as at 1 July 1986 and as at the date he gave his evidence.

Dr Armstrong made a calculation in the article of the impact of the increased risk of lung cancer occasioned by passive smoking. Extrapolating from annual cancer mortality rates in the United States of America, he estimated that as at 1983 there were 60 deaths annually in Australia due to passive smoking. The estimate was higher making a different set of assumptions.

Dr Armstrong was asked his opinion as to the value which could be attached to an epidemiological study which disclosed only a low relative risk. He accepted that it is often stated in epidemiology that relative risks of 1.5 or below are difficult to interpret. However, he said that regard must be had to the "totality of the evidence on the subject." This includes evidence, if it exists, of a trend towards increasing risk of lung cancer with increasing passive exposure to tobacco smoking. He thinks such evidence is disclosed in the Trichopoulos and Hirayama studies. Other evidence to which regard must be had is evidence of biological plausibility. In his opinion there is an inherent biological plausibility of an association between

2021550741

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

passive smoking and lung cancer. He thinks that where evidence of this kind is available, a low relative risk is not particularly important.

He was prepared to agree that, notwithstanding his opinion to the contrary, another epidemiologist could properly have held the view as at the date of publication of the advertisement that the evidence associating environmental tobacco smoke with lung cancer was equivocal. But I do not take this to be a concession that his view was not correct. Concessions of a somewhat similar kind were made by other witnesses called by the applicant. I do not think concessions of this nature are of much significance. If an opinion is erroneous, the fact that it is honestly or "properly" held does not give it validity or diminish the strength of the evidence upon which a contrary opinion is based. If that evidence establishes the correctness of the contrary opinion, then the statement of the erroneous opinion may mislead or deceive a person to whom it is made.

Of course, it might be argued that if one scientist may properly hold a certain view on a matter, the correctness of the contrary view cannot be proved scientifically. I do not find this argument persuasive insofar as it is sought to be relied upon in the present case. The respondent failed to call one witness whose special expertise is in epidemiology and of whom it could be said that he "properly" held views contrary to those expressed by the distinguished epidemiologists called by the applicant. It is a fair assumption, I think, that such a witness would have been called by the respondent had he been available. In these circumstances, the concession made by Dr Armstrong and others was little more than an admission of

2021550742

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

the theoretical possibility that another epidemiologist may hold contrary views, rather than a concession that any competent epidemiologist does in fact hold contrary views.

Dr Armstrong was cross examined at length as to the alleged deficiencies in the Hirayama and Trichopoulos studies. It is fair to say that he recognised that these and other epidemiological studies relied upon by the applicant had their limitations. But his recognition of these limitations did not cause him to alter his opinion that the totality of the evidence demonstrates a causal relationship between passive smoking and cancer.

Dr Armstrong did not agree with the proposition that an epidemiological study is not worthy of consideration unless it demonstrates a statistically significant association (T.1463). He agreed that if one is considering a single epidemiological study then the statistical significance of the data revealed by it is of great importance but he thought this was not the case if one is considering consistency among studies.

He acknowledged (T.1633) that a number of criticisms had been made of the Hirayama studies and he conceded that, to an extent, some of them were valid. He was exhaustively cross examined as to the limitations of the Hirayama and other epidemiological studies and acknowledged (T.1657) that the cross examiner had been able to raise what he described as "issues of doubt and uncertainty" in some of those studies. But he maintained his opinion that on the balance of probabilities it was correct to say that environmental tobacco smoke causes lung cancer (T.1657).

2021550743

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

(d) Professor Trichopoulos

Professor Trichopoulos is Professor of Epidemiology at the Harvard Schoo. of Public Health. He was formerly Professor and Director in the Department of Hygiene and Epidemiology at the University of Athens Medical School. He has serve. as a consultant or adviser to the World Health Organisation on, inter alia, cance: aetiology and prevention, health statistics, and epidemiology of various diseases and conditions. He has also served as a member of the Panel of Social Medicine and Epidemiology of the European Economic Community and of the Community's Special Working Group on Epidemiology and Bio-statistics. He is the author or co-author of a large number of publications including one of the primary articles referred to above.

Professor Trichopoulos responded to some of the criticisms (see infra) made by Professor Tweedie of his study. One of Professor Tweedie's criticisms was that the study excluded patients with adenocarcinomas and alveolar carcinomas. His answer was that these cell types are less associated with lung cancer in active smokers and this justified their exclusion in a study of passive smokers. He also thought that Professor Tweedie's criticism of the use of controls from a hospital for orthopaedic disorders was not justified because there was no warrant for an assumption that the wives of orthopaedic patients smoked less than others.

He also disputed that bias would have played a significant role in the results of the data collected. He claimed that at the time the study was undertaken, the doctor who conducted the interviews did not believe that passive smoking caused lung cancer and there was no public awareness of a potential link between passive

2021550744

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

smoking and lung cancer such as might have affected the answers given by patients. He accepted that in only a minority of the cases was there histological confirmation of the diagnosis of lung cancer, but he claimed that cytological diagnoses were available for two-thirds of the patients, and that such diagnoses were scientifically acceptable. He did not accept that any potential misclassification on the basis of smoking status would have changed the results of the study.

Professor Trichopoulos accepted that a critic can always point to weaknesses in a specific study, but he said that: "in epidemiology, you don't take a specific study in isolation and expect it to provide final answers on every aspect of the question." He admitted that in one important respect the result of his study had been incorrectly published in The Lancet, the journal in which it appeared. However, he said this was a typographical error and was corrected in the subsequent issue of the journal. I accept Professor Trichopoulos' evidence on this point. In the Professor's opinion, what is important about the risk ratios reported in his study is that they are statistically significant and that bias and confounding factors are reasonably excluded.

In spite of lengthy cross-examination of Professor Trichopoulos to show that he was not free from bias on the question in issue, I did not form an unfavourable impression of him in that regard. It is true that he had great difficulty in confining his answers to matters directly relevant to the questions asked of him. But I am confident that Professor Trichopoulos has great experience in the field of

2021550745

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

epidemiology and is also a man of professional integrity whose judgments are not affected by bias.

Professor Trichopoulos was criticised for not producing documents showing the data upon which his study was based. I think he might have made more effort than he did to produce these documents. However, the documents he was asked to produce were not in his custody. They were in the possession of the University of Athens. The documents were brought into existence about ten years ago. Whilst it might have been wise for him to have written to the University requesting it to make the documents available to him so that he could produce them to the respondent, he was under no obligation to do so. Moreover, I do not find it hard to believe that he thought that the request made of him was unreasonable because the class of documents he was asked to produce was very wide. It is, I think, highly unlikely that the professor and his co-authors study would have failed to have correctly analysed the data available to them.

Professor Trichopoulos agreed that his study had limitations but said that these were no different from those which he recognised himself in the text of his published article. He did not claim that his study, of itself, provided convincing evidence of a causal link between passive smoking and lung cancer. He agreed that only the convergence of results from different studies in different populations permits a reasonably sound conclusion to be drawn in that regard (T.4146-7).

2021550746

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Professor Trichopoulos' evidence was limited because of a ruling I gave as to the matters upon which he could be examined in chief. The ruling was occasioned by the fact that he was not called in the applicant's case in chief but only in reply.

(c) Professor Janerich

Professor Dwight Janerich is Professor of Epidemiology and Director of the Cancer Epidemiology Program and Cancer Prevention Research Unit at Yale University School of Medicine in New Haven, Connecticut. He is a past president of the American College of Epidemiology and has served on the Board of Directors of the College since 1979.

Professor Janerich was called to give evidence in respect of an unpublished thesis by Dr Luis Varela which was tendered by the respondent as part of its case. Dr Varela is now deceased. From 1982 to 1984 Professor Janerich was Director of the Division of Community Health and Epidemiology for the New York State Department of Health, where he was responsible for the design of the empirical study on which Dr Varela's thesis was based.

The professor explained in some detail how the data analysed by Dr Varela was collected. I do not think any good purpose would be served by a detailed account of the way in which the study was designed or the data collected. It is sufficient to say that the study appears to have been well conducted.

2021550747

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Senior counsel for he respc dent claimed, in effect, that it was not possible for him to cross examine Dr Janer h because of the absence of the raw data upon which Dr Varela's thesis w as based. I do not think that was the case. Dr Varela's thesis was tendered by t e respon ent. It is reasonable to assume it would not have been tendered if doubts were ente tained as to its validity.

There were two classes of dc uments which counsel claimed he needed in order to cross examine Professor Janer h. They were the form of questionnaire which was used in the collection of the ata, and the completed questionnaires. Professor Janerich said that the copy of tl questionnaire which was annexed to Dr Varela's thesis included all the questions v ich were relevant to the passive smoking issue. Dr Varela himself must have th ught that this was the case because he referred to only that part of the questionna e in the appendix to his study.

I am not persuaded that the ocuments, if produced, would have thrown any further light on Dr Varela's thesis or rofessor Janerich's comments upon it. It was not Dr Varela who administered t e questionnaires. This was done by interviewers employed by the New York epartment of Health. Dr Varela used data collected by the interviewers. If the questionnaires had been produced, there would have been no means of checking them to ascertain whether the answers recorded by the interviewers were corre . It is reasonable to assume that the answers were correctly recorded. I thi it must be assumed that the interviewers accurately recorded the answers communic ted to them. There is no reason to think that the interviewers were biased, dishor es or incompetent.

2021550748

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Professor Janerich said that he basically agreed with the conclusions reached by Dr Varela in his thesis. Dr Varela concluded that the data he analyzed did not show a statistically significant association between spousal smoking and lung cancer, but Professor Janerich thought there were possible explanations why this was so. He said that the evidence referred to in Dr Varela's thesis showed a positive effect and was, in his opinion, further evidence that environmental tobacco smoke can cause lung cancer. He said:

> *"The New York study is population-based and from a large catchment area, which provides important assurances for the case-control design. The study was designed to be representative of this catchment area, and we did everything we could to achieve that representiveness as the study was conducted. In my opinion, the positive finding from this study in respect of exposure to household smoking and the inability to detect a positive finding with other measures of exposure in no way detracts from the positive findings of earlier studies."*

In the light of Professor Janerich's evidence, which was virtually unchallenged, I do not think Dr Varela's thesis adds weight to the respondent's case.

(f) Sir Richard Doll

Sir Richard Doll was formerly Regius Professor of Medicine in the University of Oxford. He holds honorary degrees of Doctor of Science from Harvard, London, Oxford and other universities. He has an enviable reputation as an epidemiologist. Indeed, I think it is fair to say that many of the distinguished epidemiologists who were called in evidence regard him as something of an icon in the field of epidemiology. His academic and professional distinctions are too numerous to relate. Although he vacated his Chair at Oxford in 1979, he has maintained a close and active interest in epidemiology. He was the Director of the

2021550749

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Imperial Cancer Research Fund's Cancer Epidemiology & Clinical Trials Unit between 1978 and 1983 and between 1987 and 1989. He is currently a member of the World Health Organisation Commission on Health and Environment. He is a former member of the Council of the Royal Society and in 1986 was awarded its Royal Medal. He was the first Warden of Green College, Oxford, which was established in 1979 as a post-graduate college with a special interest in clinical medicine. His researches include studies of the health effects of smoking, ionizing radiation, and of the causes of lung cancer.

Sir Richard Doll explained the nature of epidemiological research. He said that the results obtained from such research record only associations (or the absence of associations) and, as such, may be explained in several different ways. He said that if similar associations can be produced experimentally in animals in a laboratory, it is easy to conclude that they imply causation in humans. But in the absence of such evidence interpretation of the human evidence may be difficult. However, he made it plain that, in his opinion, epidemiological evidence alone may be sufficient to establish that a factor is a cause of a disease. He said (T.3886):

> "*It is perfectly possible to draw a conclusion about causation in the absence of laboratory support. It is much more difficult and one has to require somewhat different conditions and you need a lot more thought and a lot of weight will be attached to the conclusion. Therefore, you have considerable responsibility in deciding upon the basis of epidemiological evidence alone that a factor is a cause of disease. But it can be done and has been done frequently in the past ...*"

Sir Richard Doll gave persuasive reasons supporting his opinion. He said such conclusions have been reached in the past despite the fact that intensive

2021550750

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

labor tory investigation has failed to demonstrate a similar effect in animals. He gave as ar example a conclusion which he and Professor Bradford Hill reached in 1950 that moking is an important factor in the cause of carcinoma of the lung. That conci sion was reached despite the fact that tobacco smoke had not, at that time, been recognised to be carcinogenic in animal experiments.

The evidence which was led from Sir Richard Doll was limited because he w:s called only in reply. I ruled that counsel for the applicant was not entitled to lead vidence from him as to the weight which could be attached to the data referred to in the primary articles.

Sir Richard was cross-examined for the purpose of demonstrating the extre nely cautious approach he took when seeking to ascertain whether there was proo that chemically treated oils imported into Spain as industrial oil and sold as pure olive oil were the cause of a toxic syndrome that affected many thousands of peop le in Spain in the summer of 1981. But I do not think I should infer from the cauti ous approach taken by Sir Richard in the Spanish oil disaster that he would not be s atisfied that the epidemiological evidence demonstrates a causal link between pass ve smoking and lung cancer. Consistent with my ruling as to the evidence which coul l be given by Sir Richard, it was not possible for counsel for the applicant to ask his opinion on that matter. But counsel for the respondent could have sought Sir Rich ard's opinion on it. It should not be assumed that Sir Richard's view would have bee n adverse to the applicant when his view could have been elicited by the resp ondent, but was not.

2021550751

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Sir Richard Doll was co-author with Professor Peto of an editorial which appeared in the British Journal of Cancer in 1986, in which it is stated: "Exposure to ambient smoke must be assumed to cause some lung cancers in non-smokers, as they inhale the same chemicals as smokers, and it is now generally accepted that a safe threshold is unlikely to exist for most carcinogens." This statement suggests that Sir Richard regards the biological plausibility of a link between passive smoking and lung cancer as an important adjunct to the epidemiological studies. That element of biological plausibility was absent in the Spanish oil case.

It is true that in the same editorial, having referred to reports in a number of epidemiological studies of increased lung cancer risks in the non-smoking spouses of smokers, Sir Richard Doll and Professor Peto refer to those reports as "equivocal evidence". But as I read the article, this is a reference to the reported estimates of risk, not to the presence of carcinogens in tobacco smoke and the absence of a safe threshold for them. In a letter to the British Journal of Cancer written after the publication of the editorial, Doll and Peto, referring to their previous editorial, said that in it - "we concluded that the evidence that passive smoking confers an appreciable risk, although inconclusive, is suggestive enough to justify concern." I think it is apparent from a reading of both the letter and the editorial that the authors are firmly of the view that non-smokers are exposed to an appreciable risk from passive smoking. The evidence which they regard as being equivocal and inconclusive relates to the quantification of the risk, not its existence.

2021550752

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

With reference to the concept of relative risk, Sir Richard Doll was asked whether he would agree that when a relative risk is 1.5 or below, one's confidence in causality is very much less than if it is above that number. He agreed with this proposition "in the absence of very strong other evidence" (T.3934). He said he did not accept that a risk ratio of 2 or less was necessarily evidence of a weak association (T.3951).

(g) Professor Wald

Professor Nicholas Wald is Professor and Head of the Department of Environmental and Preventive Medicine at St Bartholomew's Hospital Medical College in the University of London. He was previously Deputy Director of the Imperial Cancer Research Fund Cancer Epidemiology and Clinical Trials Unit in the University of Oxford. He is the author and co-author of a large number of publications, many of them related to research into the effects of tobacco smoking. He is a member of the United Kingdom Independent Scientific Committee on Smoking and Health, and has sat on various committees concerned with tobacco and health, including the United States National Academy of Science Committee on Passive Smoking, and the World Health Organization International Agency for Research on Cancer's Working Group on Tobacco. He was the Chairman of the United Kingdom Medical Research Council's Smoking Review Committee. He was also a member of the British Government's Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment.

2021550753

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

Professor Wald was called by the applicant to give evidence of a statistical technique sometimes described as meta-analysis. It is a statistical technique employed to combine the results of individual epidemiological studies in order to derive a quantitative summarisation of data relating to a particular area of investigation.

Professor Wald was the co-author of an article ("the Wald article") which appeared in the British Medical Journal in November 1986 in which a meta-analysis is made of many of the epidemiological studies tendered in evidence. His co-authors were a highly qualified research assistant with expertise in computer programming, a lecturer in medical statistics and a senior lecturer in cancer research who was a mathematician and epidemiologist. In his oral evidence the professor adhered to the views expressed in the article.

In meta-analysis information from several individual studies is pooled. Professor Wald said that the technique has a special value in situations where there are many studies each of which, on its own, may be too small to be expected to show an effect if there is one. There are a number of different statistical techniques for performing a meta-analysis. A somewhat similar approach to that taken in the Wald article was taken by the National Research Council in its report.

The meta-analysis in the Wald article was carried out in order to ascertain whether there is an overall association between exposure to environmental tobacco smoke and lung cancer. Professor Wald and his co-authors included only

2021550754

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

studies in which exposure was assessed by whether the subject lived with a smoker. This was done because the view was taken that such individuals were likely to be more heavily exposed to environmental tobacco smoke than non-smokers living with non-smokers. They excluded three epidemiological studies from the analysis for reasons which the professor gave. However, two of the excluded studies were consistent with the overall result achieved and the third also reported a positive effect.

Professor Wald recognised that the value of an epidemiological study may be diminished by any one of a number of errors. Of these, misclassification bias appears to me to be the most significant and, since it is a matter of considerable importance in the case, I set out in some detail what he said about it. He said in his statement of evidence:

> "13. *Examining the epidemiological evidence as a whole, particularly that relating to lung cancer among non-smokers who live with smokers compared with non-smokers who do not, there is clear evidence of an association between passive smoking and lung cancer. There are only two explanations for this association; it either represents a direct and causal effect of exposure to environmental tobacco smoke, or it may be due to systematic error (i.e. bias) or both explanations may in part apply. After careful consideration of all the potential sources of bias it can be concluded that only one source of bias must have, to some extent, exaggerated the magnitude of the observed association; this has become known as the misclassification bias. This bias will tend to introduce a spurious association between passive smoking and lung cancer. It arises from the combination of three effects. Firstly, some people who say that they are not smokers are in fact smokers, or have smoked in the past. Secondly, smokers tend to live with smokers. Thirdly, smoking is an important cause of lung cancer. It follows that in a group of reported non-smokers there will be some who, by virtue of having in fact smoked, will have a higher risk of lung cancer and also will be more likely to live with a smoker than would be the case if they were genuinely non-smokers. This will tend to produce an artefactual association between passive smoking and lung cancer among self-described non-smokers.*

2021550755

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

14. It is possible to estimate the magnitude of each of the effects that contribute to the bias, namely the proportion of misclassified smokers, the relative risk of lung cancer in those misclassified and the extent to which smokers live with smokers. With this information, together with estimates of the prevalence of smoking, one can estimate the magnitude of the bias. This reveals that the bias is very unlikely to explain the observed association between passive smoking and lung cancer. In my opinion, the observed association could only be completely explained in this way if unreasonably high estimates of the magnitude of the effects that contribute to the bias were used.

15. The validity of the misclassification bias depends on the close association between active smoking and lung cancer, an association that is accepted by scientists as being causal. Invoking the bias accepts this link between active smoking and lung cancer as well as the need to revise the observed relative risk between passive smoking and lung cancer to allow for the bias. It is illogical to accept it for one purpose but not for the other. It illustrates the importance of considering the evidence on lung cancer in relation to active and passive smoking together, recognizing the qualitative similarities in the two exposures and the expectation that a little of what causes a large increase in risk will still cause an increase in risk, albeit to a smaller extent. It also demonstrates how it is necessary when judging whether the association between passive smoking and lung cancer is causal to have an informed view on this issue with respect to active smoking and lung cancer. To hold a view on the former without holding one on the latter is logically untenable."

The meta-analysis carried out in the Wald article showed that there was a highly significant 35% increase in the risk of lung cancer among non-smokers living with smokers compared with non-smokers living with non-smokers. The relative risk of 1.35 was statistically significant at the 95% confidence interval. The authors of the study recognised that misclassification of some smokers as non-smokers had probably exaggerated the estimated increase in risk. Adjustment for this error reduced their estimated relative risk to 1.30. However, as people who live with non-smokers may still be exposed to other people's smoke they revised this estimate again to allow for the fact that a truly unexposed reference group was not used. The increase in risk

2021550756

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

among non-smokers living with smokers compared with the completely unexposed group was thus estimated by them as 53%, i.e. a relative risk of 1.53.

I have already referred to the fact that the National Research Council carried out a somewhat similar exercise. In the NRC report the relative risk of "exposed" non-smokers compared with truly "unexposed" non-smokers is stated to be 1.42.

The authors of the Wald article stated their conclusions in the following terms:

> "*We conclude that breathing other people's tobacco smoke does cause lung cancer, and our conclusion rests on several observations. Firstly, carcinogens in tobacco smoke are released into the air. Secondly, tobacco smoke is breathed into the lungs by non-smokers. Thirdly, the general view is that exposure to carcinogens does not have a threshold below which there is no effect. Fourthly, people known to have an increased exposure to environmental tobacco smoke seem to have an excess risk of lung cancer, which is not explained satisfactorily by bias. Fifthly, the magnitude of the excess seems reasonable in view of the extent of exposure and, sixthly, there is a dose response relation between the extent of exposure and risk. In view of all these observations, we could not have concluded otherwise.*"

The authors estimated that about a third of the cases of lung cancer in non-smokers who lived with smokers, and about a quarter of the cases in non-smokers in general, may be attributed to exposure to environmental tobacco smoke.

Professor Tweedie (a witness called the respondent) identified potential sources of bias in most, if not all, of the epidemiological studies upon which the Wald meta-analysis is based. Professor Wald agreed that it is always possible that any

2021550757

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

epidemiological study may be affected by bias, but he did not think that this potentiality affected the validity of the exercise which he and his co-authors carried out. He said that the real issue is not whether there is a potentiality for bias. Rather, it is whether there is error of such character and magnitude that it has systematically disordered the results of the study in such a way as to lead to an association between passive smoking and lung cancer that would not otherwise have been observed. He said this had not been shown to have been the case. In particular, he did not think that Professor Tweedie's criticisms of the Hirayama and Trichopoulos studies showed them to be so flawed as to warrant their exclusion from the meta-analysis exercise. The voluminous evidence on this issue (and many other issues) is impossible to summarise in these reasons. However, I find Professor Wald's evidence on this matter most persuasive and I do not think that his meta-analysis was shown to be seriously flawed. As I have observed, the result of it is not greatly different from a similar exercise carried out by the National Research Council.

Dr Layard, another witness called by the respondent, expressed the opinion that the epidemiological studies upon which the Wald article is based lack consistency. Professor Wald holds a different view. In his opinion the undoubted variation in the point estimates in the studies is consistent with the sort of random variation that one would expect from a number of studies.

Dr Layard thinks that the utility of meta-analysis is very limited and that studies cannot be combined in a meta-analysis if the results in any of them may be due to bias or confounding. Professor Wald agreed that any epidemiological study

2021550758

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

which is so flawed as to make it uninformative should not be used as evidence, whether alone or in combination with other studies, in making a meta-analysis. However, he thinks that a study that is sufficiently sound to be considered as evidence on its own is eligible for inclusion in a meta-analysis. He agreed that a flawed study cannot be improved by inclusion in a meta-analysis. But he thinks that a sound study, albeit too small to show an effect on its own, can be used with other studies to show an effect. He agreed that meta-analysis cannot overcome bias, but said it can be used to overcome random error from small numbers in small studies.

Professor Wald was careful to point out that the risk ratio derived from a meta-analysis is a "summary estimate" of a given effect. That is to say, it is not the measure of the effect which will be applicable in all situations surveyed in all the epidemiological studies upon which the meta-analysis is based. In some social groups, exposure to environmental tobacco smoke may be more intense than in others and in these one would expect the effect of exposure to be greater. He illustrated his view by the observation that since room sizes in Japan are smaller on average than in the United States, exposure to environmental tobacco smoke in Japan is greater than in the United States. Hence one would expect that the relative risk estimate would be greater in the Japanese studies than in the American studies. But he thought that differences of this kind were no reason to conclude that the two sets of data cannot be combined to obtain an overall summary effect or to ascertain the overall level of statistical significance.

2021550759

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

On a separate matter, Professor Wald said that cotinine is a reasonably sensitive measure of exposure to passive smoke and that it has many advantages in that respect over other markers (T.4352). He accepted that estimates of doses of tobacco smoke based upon cotinine measurements need to be considered cautiously (T.4404). He agreed that mainstream and environmental tobacco smoke differ in some respects, but thought that their similarities are more striking than their differences (T.4404).

On another separate matter, Professor Wald expressed the opinion that Dr Varela's thesis, which formed part of the respondent's case, lent some weight to the conclusion that passive smoking causes lung cancer. He accepted that the data analysed by Dr Varela are consistent both with no association between lung cancer and exposure to environmental tobacco smoke in the home and with the positive association reported in both his meta-analysis and the NRC report. However, he drew attention to Dr Varela's examination of the association between exposure to environmental tobacco smoke as measured by the total number of smokers in the household expressed in terms of the number of person-years of passive smoke exposure. This examination showed a statistically significant association between such exposure and lung cancer. These apparently inconsistent results suggested to him that in some studies spousal smoking alone may be a poor way of categorising a person's exposure to environmental tobacco smoke.

As is apparent from the statement of the conclusions in the Wald article, Professor Wald's opinion that passive smoking is a cause of lung cancer is by

2021550760

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

no means based only on the statistically significant association he and his co-authors found between lung cancer and passive smoking. I think the difference between his views and those of the other epidemiologists called by the applicant, and the views of witnesses called by the respondent is explained by the broader approach taken by the former group of witnesses.

Professor Wald and the other witnesses called by the applicant tended to regard the separate items of scientific material (e.g. epidemiological studies, the "no threshold" for carcinogens theory, the presence of carcinogens in environmental tobacco smoke, and cotinine levels in non-smokers) as constituent parts of a mosaic, each piece itself representing some evidence that environmental tobacco smoke causes cancer in non-smokers. On the other hand, the respondent's witnesses tended to evaluate each piece of evidence in isolation. I think therein lies the explanation for much of the collision of opinion between the witnesses for the parties.

Professor Wald sees the epidemiologist as one of a team, the members of which collaborate in reaching a judgment. He said (T.4251):

> "*I am an epidemiologist. I am not a mathematician or a statistician, but epidemiologists by nature of their work collaborate closely with biologists, scientists, clinicians, statisticians and work together with them as a team, and in much of the work I do their components are performed by colleagues and the responsibility for the different components will vary depending on the different skills. In computing the mathematical calculations that are involved in some of these analyses I rely heavily on statistical colleagues as do many - in fact all my epidemiological colleagues, Richard Doll, Prof. Trichopoulos and others. But at the end of the day I have to satisfy myself that what has been performed by my colleagues is sound and is a correct reflection of the scientific position and have to accept the responsibility for it, but I cannot say that I do every*

0221550761

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000

component bit of calculation. Indeed nor do they. They rely very much on other contributions in order to reach their judgments."

I was left with the impression that Professor Tweedie and Dr Layard do not take the same approach to their discipline, which is the science of statistics. I am inclined to think that they tended to work within their own discipline and that, accordingly, they tended to take a narrower approach when considering whether the whole of the available data warranted a conclusion as to a causal link between passive smoking and lung cancer.

I have already observed that Professor Wald was a member of the National Research Council's Committee on Passive Smoking which produced the NRC report. He prepared the first draft of Chapter 12 of the report, which deals with exposure to environmental tobacco smoke and lung cancer. He said that his draft was worked on by others and also sent informally to scientific referees. Before the report was published it was sent to independent experts to judge whether it was in a satisfactory form. He said that he agreed with the general conclusions in the document as finally settled, and that he still adhered to the views expressed in it (T.4362).

(h) Dr Layard

Dr Maxwell Layard is a partner in a firm of consulting statisticians based in California. He was formerly an Assistant Professor of Mathematics at the University of California. From 1973 to 1979 he was a statistician in the Mathematical Statistical and Applied Mathematics Section of the National Cancer Institute. From

2021550762

Source: https://www.industrydocuments.ucsf.edu/docs/rxvl0000